FILE 'REGISTRY' ENTERED AT 09:33:57 ON 07 NOV 2002
E HEAT SHOCK PROTEIN/CN
L1 524 S HEAT SHOCK PROTEIN?/CN
E HEAT SHOCK PROTEIN 65/CN
E BACTERIAL HEAT SHOCK PROTEIN/CN

FILE 'HCAPLUS' ENTERED AT 09:36:19 ON 07 NOV 2002
L1 524 SEA FILE=REGISTRY ABB=ON PLU=ON HEAT SHOCK PROTEIN?/CN

L2 17545 SEA FILE=HCAPLUS ABB=ON PLU=ON L1 OR HSP OR HEAT SHOCK PROTEIN OR HSP65 OR HSP70 OR HSP90
L5 22 SEA FILE=HCAPLUS ABB=ON PLU=ON L2 AND (CD8 OR CD 8)(1W)(CTL OR CYTOTOX? T LYMPHOCYT?)
L6 22 SEA FILE=HCAPLUS ABB=ON PLU=ON L5 AND (PROTEIN OR PEPTIDE OR POLYPROTEIN OR POLYPEPTIDE OR GLYCOPROTEIN OR CARBOHYDRATE OR ANTIGEN OR LIPID)

L6 ANSWER 1 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:595035 HCAPLUS
DOCUMENT NUMBER: 137:168254
TITLE: Superior molecular vaccine based on self-replicating RNA, suicidal DNA or naked DNA vector, that links **antigen** with **polypeptide** that promotes **antigen** presentation for treating cancer and infections
INVENTOR(S): Wu, Tzyy-Choou; Hung, Chien-Fu
PATENT ASSIGNEE(S): The Johns Hopkins University, USA
SOURCE: PCT Int. Appl., 127 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002061113	A2	20020808	WO 2002-US2598	20020201

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-265334P P 20010201

AB Improved mol. vaccines comprise nucleic acid vectors that encode a fusion **polypeptide** that includes **polypeptide** or **peptide** phys. linked to an **antigen**. The linked **polypeptide** is one that (a) promotes processing of the expressed fusion **polypeptide** via the MHC class I pathway and/or (b) promotes development or activity of **antigen** presenting cells, primarily dendritic cells. These vaccines employ one of several types of nucleic acid vectors, each with its own

relative advantages: naked DNA plasmids, self-replicating RNA replicons and suicidal DNA-based on viral RNA replicons. Administration of such a vaccine results in enhance immune responses, primarily those mediated by **CD8+ cytotoxic T lymphocytes**, directed against the immunizing **antigen** part of the fusion **polypeptide**. Such vaccines are useful against tumor **antigens**, viral **antigens** and **antigens** of other pathogenic microorganisms and can be used in the prevention or treatment of diseases that include cancer and infections.

L6 ANSWER 2 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:3750 HCAPLUS
DOCUMENT NUMBER: 137:153537
TITLE: Induction of specific cytotoxic T lymphocytes using hepatoma antigenic **peptide** mixed with **HSP70** in vitro
AUTHOR(S): Guo, Ailin; Sui, Yanfang; Qu, Ping; Zhang, Lihong; Ye, Jing; Wang, Xiaoping
CORPORATE SOURCE: Department of Pathology, Fourth Military.Medical University, Xi'an, 710032, Peop. Rep. China
SOURCE: Zhongguo Mianyixue Zazhi (2001), 17(11), 584-586, 592
CODEN: ZMZAEE; ISSN: 1000-484X
PUBLISHER: Zhongguo Mianyixue Zazhi Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB The possibility of inducing cell-mediated immune response with **HSP70**-antigenic **peptide** complex in vitro was studied. **HSP70-peptide** complex was reconstituted in vitro. Granulocyte/macrophage colony stimulating factors and interleukin 4 were used to cultivate dendritic cells (DC) from peripheral blood of HLA-A2 pos. healthy donors. **HSP70**, **HSP70-peptide** complex, or **peptide** was used to activate the DC individually, which will initiate to homogenize T lymphocyte to form cytotoxic T lymphocyte (CTL). The cytotoxicity of the CTL was detected by MTT assay. It was found that **peptide**-specific **CD8+ CTL** responses were readily elicited by **HSP70-peptide** complex or **peptide**. The CTL response primed by **HSP70-peptide** complex was more potent than **peptide** alone. The results suggested that **HSP70-peptide** complex as immunogenic **HSP70** can cause great efficient CTL response, and antigenic **peptides** and **HSP70** complex may be used as **peptide** vaccines for cancer immunotherapy.

L6 ANSWER 3 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:2569 HCAPLUS
DOCUMENT NUMBER: 137:45494
TITLE: The involvement of class Ib molecules in the host response to infection with Salmonella and its relevance to autoimmunity
AUTHOR(S): Soloski, Mark J.; Metcalf, Eleanor S.
CORPORATE SOURCE: Department of Medicine and The Graduate Program in Immunology, Division of Rheumatology, The Johns Hopkins University School of Medicine, Baltimore, MD, 21218, USA

SOURCE: Microbes and Infection (2001), 3(14-15), 1249-1259
CODEN: MCINFS; ISSN: 1286-4579
PUBLISHER: Editions Scientifiques et Medicales Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Class I mols. with limited polymorphism have been implicated in the host response to infectious agents. Following infection with Salmonella typhimurium, mice develop a **CD8+ CTL** response that specifically recognizes bacteria infected cells. An immunodominant component of the CTL response recognizes a **peptide** epitope derived from the Salmonella GroEL mol. that is presented by the non-polymorphic MHC class Ib mol. Qa-1. T cells recognizing the bacterial **peptide** also cross-recognize a homologous **peptide** from the mammalian hsp60 mol. Since Qa-1 has a functional equiv. in humans, this observation may be relevant not only to the host response involved in clearing infection but also in understanding the link between infection with Gram-neg. pathogens and autoimmune disease.

REFERENCE COUNT: 120 THERE ARE 120 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:714078 HCAPLUS
DOCUMENT NUMBER: 136:4428
TITLE: DNA immunization with Trypanosoma cruzi **HSP70** fused to the KMP11 **protein** elicits a cytotoxic and humoral immune response against the **antigen** and leads to protection
AUTHOR(S): Planelles, Lourdes; Thomas, M. Carmen; Alonso, Carlos; Lopez, Manuel C.
CORPORATE SOURCE: Departamento de Biologia Molecular, Instituto de Parasitologia y Biomedicina "Lopez Neyra," CSIC, Granada, 18001, Spain
SOURCE: Infection and Immunity (2001), 69(10), 6558-6563
CODEN: INFIBR; ISSN: 0019-9567
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Murine immunization with Trypanosoma cruzi KMP11-**HSP70** fused genes but not the KMP11 gene alone elicited both an IgG2a long-lasting humoral immune response against KMP11 **protein** and activation of **CD8+ cytotoxic T lymphocytes** specific for two KMP11 **peptides** contg. A2 motifs. Moreover, protection against the parasite challenge was obsd. after immunization with the chimeric gene.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:525946 HCAPLUS
DOCUMENT NUMBER: 135:136405
TITLE: In vivo CTL elicitation by **heat shock protein** fusion **proteins** maps to a discrete ATP binding

domain and is CD4+ T cell-independent

INVENTOR(S): Huang, Qian; Richmond, Joan F. L.; Cho, Bryan K.; Palliser, Deborah; Chen, Jianzhu; Eisen, Herman N.; Young, Richard A.

PATENT ASSIGNEE(S): Whitehead Institute for Biomedical Research, USA; Massachusetts Institute of Technology

SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001051081	A1	20010719	WO 2000-US32831	20001201
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1253939	A1	20021106	EP 2000-980947	20001201
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2002146426	A1	20021010	US 2001-761534	20010116

PRIORITY APPLN. INFO.: US 2000-176143P P 20000114
WO 2000-US32831 W 20001201

AB The present invention relates to a method of inducing a **CD8** + **CTL** response to a mol. in an individual deficient in CD4+ T cells comprising administering to the individual an **hsp** or a portion of an ATP binding domain of an **hsp** joined to the mol. In one embodiment, the present invention relates to a method of treating HIV in an individual deficient in CD4+ T cells comprising administering to the individual an **hsp** or a portion of an ATP binding domain of an **hsp** joined to the mol. Also encompassed by the present invention is a method of inducing a CD4+ independent CTL response in an individual comprising administering to the individual a portion of an ATP binding domain of an **hsp** joined to the mol. The present invention also relates to a method of inducing a **CD8+ CTL** response in an individual comprising administering to the individual a portion of an ATP binding domain of an **hsp** joined to the mol. In addn., the present invention relates to a compn. characterized by a portion of an ATP binding domain of an **hsp** joined to a mol.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:524561 HCAPLUS
DOCUMENT NUMBER: 136:52446

TITLE: Tumor rejection by secreted heat shock fusion **protein** and CTL
AUTHOR(S): Yamazaki, Koichi
CORPORATE SOURCE: First Department of Internal Medicine, Hokkaido University, Japan
SOURCE: Annual Review Men'eki (2001) 308-316
CODEN: ARMNCI
PUBLISHER: Chugai Igakusha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review on secreted heat shock fusion **protein** mediated tumor rejection through induction of cytotoxic T lymphocytes. Role of **heat shock proteins** in tumor rejection **antigen** processing and presentation to MHC class I mols., **heat shock protein**-based vaccines, induction of **heat shock protein** expression by gene transfer and enhanced immunogenicity, construction of secreted heat shock fusion **protein** gp96-Ig, tumor rejection induced by transduction of gp96-Ig cDNA through induction of **CD8+ cytotoxic T lymphocytes**, and use of secreted heat shock fusion **proteins** in immunotherapy are discussed.

L6 ANSWER 7 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:212805 HCAPLUS
DOCUMENT NUMBER: 134:365438
TITLE: The ability of heat-killed Mycobacterium vaccae to stimulate a cytotoxic T-cell response to an unrelated **protein** is associated with a 65 kilodalton **heat-shock protein**
AUTHOR(S): Skinner, M. A.; Prestidge, R.; Yuan, S.; Strabala, T. J.; Tan, P. L. J.
CORPORATE SOURCE: Genesis Research and Development Corporation Ltd, Auckland, N. Z.
SOURCE: Immunology (2001), 102(2), 225-233
CODEN: IMMUAM; ISSN: 0019-2805
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Exogenous **antigens** are generally presented by Class II major histocompatibility (MHC) mols. When administered with an adjuvant, however, they are capable of inducing a CD8+ T-cell response where **antigen** recognition is assocd. with Class I MHC. Accordingly, immunization with sol. ovalbumin (OVA) alone does not activate CD8+ cytotoxic T cells (CTL) but when given in complete Freund's adjuvant (CFA), or in formulations of a no. of novel adjuvants, an OVA-specific **CD8+ CTL** response can be detected. We show in this report that immunization with sol. OVA mixed with heat-killed Mycobacterium vaccae, but not with other common pathogenic and saprophytic mycobacteria, can activate OVA-specific **CD8+ CTL**. An OVA-specific CTL response is detected when mice are immunized by either the i.p. or intranasal route and their spleen cells are re-stimulated in vitro. Adjuvant activity of heat-killed M. vaccae is present in M. vaccae culture filtrate, in sol. **protein** components of whole M. vaccae and in the 65 kDa **heat-shock protein (hsp)** of M. vaccae. Mycobacterium vaccae

has previously been shown to have no adverse side-effects in humans. The current results suggest that M. vaccae may be useful as an adjuvant for vaccines and other immunotherapies where **CD8+ CTL** responses to exogenous **proteins** are crucial.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 8 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:160814 HCAPLUS
DOCUMENT NUMBER: 135:271320
TITLE: Unraveling the mechanisms by which **heat shock proteins** activate the immune system
AUTHOR(S): Palliser, Deborah
CORPORATE SOURCE: Center for Cancer Research and Department of Biology, Massachusetts Institute of Technology, Cambridge, MA, 02139, USA
SOURCE: Current Opinion in Molecular Therapeutics (2001), 3(1), 25-30
CODEN: CUOTFO; ISSN: 1464-8431
PUBLISHER: PharmaPress Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 37 refs. A role for **heat shock proteins** in eliciting **CD8 cytotoxic T-lymphocyte** (CTL) responses in the absence of exogenous adjuvants has been documented for some time. Only recently, however, has the mechanism by which these mols. are able to elicit such responses begun to be elucidated. This review discusses the possible mechanisms by which **heat shock proteins** stimulate CTLs.
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 9 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:241793 HCAPLUS
DOCUMENT NUMBER: 133:16081
TITLE: A proposed mechanism for the induction of cytotoxic T lymphocyte production by heat shock fusion **proteins**
AUTHOR(S): Cho, Bryan K.; Palliser, Deborah; Guillen, Eduardo; Wisniewski, Jan; Young, Richard A.; Chen, Jianzhu; Eisen, Herman N.
CORPORATE SOURCE: Center for Cancer Research and Department of Biology, Massachusetts Institute of Technology, Cambridge, MA, 02139, USA
SOURCE: Immunity (2000), 12(3), 263-272
CODEN: IUNIEH; ISSN: 1074-7613
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A 65 kDa mycobacterial **heat shock protein (hsp65)**, fused to a **polypeptide** that contains an octapeptide (SIYRYYGL) agonist for a particular T cell receptor (2C TCR), stimulated C57BL/6 mice as well as CD4-deficient mice to produce CD8+ cytolytic T lymphocytes (CTL) to

the fusion partner's octapeptide. This and other **hsp65** fusion **proteins** but not native **hsp65** itself stimulated dendritic cells in vitro and in vivo to upregulate the levels of MHC (class I and II) and costimulatory (B7.2) mols. The results suggest a mechanism for the general finding that **hsp** fusion **proteins**, having fusion partners of widely differing lengths and sequences, elicit **CD8 CTL** to **peptides** from the fusion partners without requiring exogenous adjuvants or the participation of CD4+ T cells.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 10 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:154208 HCAPLUS
DOCUMENT NUMBER: 132:292432
TITLE: Recombinant adeno-associated virus expressing human papillomavirus type 16 E7 **peptide** DNA fused with **heat shock protein** DNA as a potential vaccine for cervical cancer
AUTHOR(S): Liu, Dai-Wei; Tsao, Yeou-Ping; Kung, John T.; Ding, Yu-An; Sytwu, Huey-Kang; Xiao, Xiao; Chen, Show-Li
CORPORATE SOURCE: Department of Microbiology and Immunology, National Defense Medical Center, Taipei, Taiwan
SOURCE: Journal of Virology (2000), 74(6), 2888-2894
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In this study, the authors explore a potential vaccine for human papillomavirus (HPV)-induced tumors, using **heat shock protein** as an adjuvant, a **peptide** vaccine for safety, and adeno-assocd. virus (AAV) as a gene delivery vector. The tumor vaccine was devised by constructing a chimeric gene which contained HPV type 16 E7 cytotoxic T-lymphocyte (CTL) epitope DNA fused with the **heat shock protein** gene as a tumor vaccine delivered via AAV. The results demonstrate that this vaccine can eliminate tumor cells in syngeneic animals and induce CD4- and **CD8**-dependent **CTL** activity in vitro. Moreover, studies with knockout mice with distinct T-cell deficiencies confirm that CTL-induced tumor protection is CD4 and CD8 dependent. Taken together, the evidence indicates that this chimeric gene delivered by AAV has potential as a cervical cancer vaccine.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 11 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:85906 HCAPLUS
DOCUMENT NUMBER: 132:235665
TITLE: Molecular mimicry mediated by MHC class Ib molecules after infection with gram-negative pathogens
AUTHOR(S): Lo, Wei-Feng; Woods, Amina S.; DeCloux, Amy; Cotter, Robert J.; Metcalf, Eleanor S.; Soloski,

Mark J.
CORPORATE SOURCE: Division of Rheumatology, Department of Medicine and The Graduate Program in Immunology, The Johns Hopkins University School of Medicine, Baltimore, MD, 21218, USA
SOURCE: Nature Medicine (New York) (2000), 6(2), 215-218
CODEN: NAMEFI; ISSN: 1078-8956
PUBLISHER: Nature America
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The development of many autoimmune diseases has been etiol. linked to exposure to infectious agents. For example, a subset of patients with a history of Salmonella infection develop reactive arthritis. The persistence of bacterial **antigen** in arthritic tissue and the isolation of Salmonella or Yersinia reactive CD8+ T cells from the joints of patients with reactive arthritis support the etiol. link between Gram-neg. bacterial infection and autoimmune disease. Models proposed to account for the link between infection and autoimmunity include inflammation-induced presentation of cryptic self-epitopes, **antigen** persistence and mol. mimicry. Several studies support mol. mimicry as a mechanism for the involvement of class II epitopes in infectious disease-induced self-reactivity. Here, the authors have identified an immunodominant epitope derived from the S. typhimurium GroEL mol. This epitope is presented by the mouse H2-T23-encoded class Ib mol. Qa-1 and was recognized by **CD8+ cytotoxic T lymphocytes** induced after natural infection. S. typhimurium-stimulated cytotoxic T lymphocytes recognizing the GroEL epitope cross-reacted with a **peptide** derived from mouse **heat shock protein** 60 and recognized stressed macrophages. The results indicate involvement of MHC class Ib mols. in infection-induced autoimmune recognition and indicate a mechanism for the etiol. link between Gram-neg. bacterial infection and autoimmunity.
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 12 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:71361 HCAPLUS
DOCUMENT NUMBER: 132:221039
TITLE: In vivo cytotoxic T lymphocyte elicitation by mycobacterial **heat shock protein** 70 fusion **proteins** maps to a discrete domain and is CD4+ T cell independent
AUTHOR(S): Huang, Qian; Richmond, Joan F. L.; Suzue, Kimiko; Eisen, Herman N.; Young, Richard A.
CORPORATE SOURCE: Whitehead Institute for Biomedical Research, Cambridge, MA, 02142, USA
SOURCE: Journal of Experimental Medicine (2000), 191(2), 403-408
CODEN: JEMEAV; ISSN: 0022-1007
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To gain insights into the mechanisms by which sol. **heat shock protein** (**hsp**) fusions can elicit

CD8+ cytotoxic T lymphocytes (CTLs) against the fusion partner, mycobacterial (M. tuberculosis) **hsp70** was dissected to ascertain whether a particular **hsp** domain is necessary, and knockout mice were used to det. whether the fusion **protein**'s immunogenicity is dependent on CD4+ T lymphocytes. The authors found that the ability to elicit **CD8+ CTLs** depends on a discrete 200-amino acid **protein** domain, indicating that the fusion **protein** 's immunogenicity for CD8+ T cells does not require coupled chaperone function or **peptide** binding. Further, the authors found that ovalbumin (OVA).**hsp70** fusion **protein** elicited anti-OVA **CD8+ CTLs** about equally well in CD4 knockout and wild-type C57BL/6 mice, and also when the **hsp70** was of murine (self) origin. The ability of **hsp70** fusion **proteins** to elicit CD4-independent CTL responses suggests that **hsp70** fusion **proteins** may be useful for immunol. prophylaxis and therapy against disease in CD4+ T cell-deficient individuals.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 13 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:736761 HCAPLUS
DOCUMENT NUMBER: 132:48909
TITLE: Cutting edge: Tumor secreted heat shock-fusion **protein** elicits CD8 cells for rejection
AUTHOR(S): Yamazaki, Koichi; Nguyen, Timmy; Pokack, Eckhard R.
CORPORATE SOURCE: Department of Microbiology and Immunology, University of Miami School of Medicine, Miami, FL, 33101, USA
SOURCE: Journal of Immunology (1999), 163(10), 5178-5182
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The endoplasmic reticulum resident **heat shock protein** gp96 chaperons **peptides**, including those derived from tumor Ags, on their way to presentation by MHC class I. Replacement of the endoplasmic reticulum retention signal of gp96 with the Fc portion of murine IgG1 generated a secretory form of gp96, gp96-Ig. Tumor cells secreting gp96-Ig exhibited decreased tumorigenicity and increased immunogenicity in vivo and were rejected after initial growth. Rejection required CD8 T cells during the priming and effector phase. CD4 T cells were not required for rejection in either phase. Carrageenan, a compd. known to inactivate macrophages in vivo, did not diminish CD8-mediated tumor rejection. Therefore, immunization with tumors secreting gp96-Ig generates efficient tumor-rejecting **CD8 CTL** without requirement for CD4 or macrophage help. In contrast, immunization with purified, tumor-derived gp96 or with irradiated tumor cells requires both.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 14 OF 22 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:43518 HCAPLUS
DOCUMENT NUMBER: 130:250870
TITLE: Priming of **CD8+ CTL** effector cells in mice by immunization with a stress **protein**-influenza virus nucleoprotein fusion molecule
AUTHOR(S): Anthony, Lawrence S. D.; Wu, Huacheng; Sweet, Heather; Turnnir, Cor; Boux, Leslie J.; Mizzen, Lee A.
CORPORATE SOURCE: StressGen Biotechnologies Corporation, Victoria, BC, V8Z 4B9, Can.
SOURCE: Vaccine (1998), Volume Date 1999, 17(4), 373-383
CODEN: VACCDE; ISSN: 0264-410X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Literature is accumulating which suggests the potential for stress **proteins** to form the basis of a novel vaccine technol. Immunization with mammalian tumor-derived stress **proteins** and their assocd. **peptides** promote anti-tumor immunity. Vaccination with HIV-1 p24 **antigen** fused to mycobacterial **heat shock protein** (**Hsp**) Hsp71 enhances p24-specific immunity, as measured by p24-specific antibody prodn. and in vitro cell proliferation and cytokine induction. An ovalbumin-Hsp71 fusion **protein** primes ovalbumin-specific CTL activity and resistance to challenge with an ovalbumin-expressing tumor. The authors have extended these observations by using a mycobacterial **Hsp65** fusion mol. to prime CTL specific for a viral **antigen**. Gene fusion constructs were generated from DNA encoding Mycobacterium bovis strain BCG **Hsp65** and individual fragments of influenza virus nucleoprotein (NP) encompassing H-2Kd-and H-2Db-restricted CTL epitopes. The ability of these purified recombinant fusion **proteins** to prime NP-specific CTL was assessed in mice of appropriate H-2 haplotypes. The authors obsd. that adjuvant-free immunization with either fusion **protein** elicited significant CTL activity when administered at doses of 10-100 .mu.g per mouse. An NP fusion **protein** made with glutathione-S-transferase failed to elicit NP-specific CTL, indicating that the phenomenon requires **Hsp65** sequences. A single immunization with the **Hsp65**-NP fusion **protein** elicited CTL activity which persisted for a min. of 4 mo post-immunization, at which time it could be boosted by a second immunization. To the authors' knowledge, this is the first report of a member of the Hsp60 family priming for **antigen** -specific CTL activity when employed as a fusion **protein** partner.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 15 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:765905 HCAPLUS
DOCUMENT NUMBER: 130:166982
TITLE: Interferon-gamma (IFN-.gamma.) and tumor necrosis factor-alpha (TNF-.alpha.) are necessary in the early stages of induction of CD4 and CD8 cytotoxic T cells by Mycobacterium

leprae **heat shock**
protein (hsp) 65 kD

AUTHOR(S): Sasiain, M. del C.; De La Barrera, S.; Fink, S.; Finiasz, M.; Aleman, M.; Farina, M. H.; Pizzariello, G.; Valdez, R.
CORPORATE SOURCE: Departamento de Inmunologia, IIHema., Academia Nacional de Medicina, Buenos Aires, 1425, Argent.
SOURCE: Clinical and Experimental Immunology (1998), 114(2), 196-203
CODEN: CEXIAL; ISSN: 0009-9104
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cytotoxic T cells (CTL) may play an important role in host defense against mycobacterial infections. CD4 CTL are preferentially induced by mycobacteria, but both CD4 and **CD8 CTL** may be necessary components of a protective immune response. The 65-kD mycobacterium **heat shock protein** (**hsp65**) is a poor inducer of CTL in multi-bacillary leprosy (MB) patients. In this study we evaluate the possible role of cytokines in modulating the cytotoxic activity of CTL from leprosy patients and normal individuals (N) against autologous macrophages presenting Mycobacterium leprae **hsp65**. Our results show that **hsp65**-specific CTL were generated from both CD4 and CD8 lymphocytes. In N, individual cytokines as well as the combination of them were able to modify the **hsp65** -induced cytotoxic activity. The effect of cytokines on leprosy patients' lymphocytes was different in MB and paucibacillary (PB) patients. Thus, IL-6, IL-2, IFN-.gamma. or TNF-.alpha. did not modify the generation of **hsp65**-CTL from either MB (with or without an erythema nodosum episode (ENL)) or PB. In all the patients the simultaneous addn. of two cytokines was required in order to increase CTL generation. In MB, IL-6 plus IFN-.gamma. or IL-2 increased both CD4 and **CD8 CTL**, while TNF-.alpha. plus IFN-.gamma. up-regulated only CD4 CTL. In PB, **CD8 CTL** were prominent with IL-6 plus IFN-.gamma., while the increase was significant in CD4 CTL with IL-6 plus IL-2. Down-regulation of CTL was obsd. by addn. of IL-4, IL-10, anti-IFN-.gamma. or anti-TNF-.alpha. in N controls. Our data demonstrate that IFN-.gamma. and TNF-.alpha. must be present for at least the first 60 h of the induction stage in order to generate full **hsp65** CTL. Hence, IFN-.gamma. and TNF-.alpha. would be key factors in the generation of **hsp65** CTL.
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 16 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:792541 HCAPLUS
DOCUMENT NUMBER: 128:74058
TITLE: Heat shock fusion **proteins** as vehicles for **antigen** delivery into the major histocompatibility complex class I presentation pathway
AUTHOR(S): Suzue, Kimiko; Zhou, Xianzheng; Eisen, Herman N.; Young, Richard A.
CORPORATE SOURCE: Nine Cambridge Center, Whitehead Institute for

Biomedical Research, Cambridge, MA, 02142, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1997), 94(24), 13146-13151
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mice immunized with **heat shock proteins** (**hsps**) isolated from mouse tumor cells (donor cells) produce **CD8 cytotoxic T lymphocytes** (CTL) that recognize donor cell **peptides** in assocn. with the major histocompatibility complex (MHC) class I **proteins** of the responding mouse. The CTL are induced apparently because **peptides** noncovalently assocd. with the isolated **hsp** mols. can enter the MHC class I **antigen** processing pathway of professional **antigen** -presenting cells. Using a recombinant heat shock fusion **protein** with a large fragment of ovalbumin covalently linked to mycobacterial **hsp70**, the authors show here that when the sol. fusion **protein** was injected without adjuvant into H-2b mice, CTL were produced that recognized an ovalbumin-derived **peptide**, SIINFEKL, in assocn. with Kb. The **peptide** is known to arise from natural processing of ovalbumin in H-2b mouse cells, and CTL from the ovalbumin-**hsp70**-immunized mice and a highly effective CTL clone (4G3) raised against ovalbumin-expressing EL4 tumor cells (EG7-OVA) were equally effective in terms of the concn. of SIINFEKL required for half-maximal lysis in a CTL assay. The mice were also protected against lethal challenge with ovalbumin-expressing melanoma tumor cells. Because large **protein** fragments or whole **proteins** serving as fusion partners can be cleaved into short **peptides** in the MHC class I processing pathway, **hsp** fusion **proteins** of the type described here are promising candidates for vaccines aimed at eliciting **CD8** **CTL** in populations of MHC-disparate individuals.

L6 ANSWER 17 OF 22 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1997:299378 HCAPLUS
DOCUMENT NUMBER: 126:272363

TITLE: Treatment or prevention of neoplastic and infectious diseases with immune response-augmenting heat shock/stress **protein** complexes, method for measuring tumor rejection, and **heat** **shock protein** 70- **peptide** complex purification

INVENTOR(S): Srivastava, Pramod K.
PATENT ASSIGNEE(S): Fordham University, USA

SOURCE: PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9710001	A1	19970320	WO 1996-US14557 19960911
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, FI, GE, HU, IL, IS, JP, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
US 5837251	A	19981117	US 1995-527391 19950913
AU 9670181	A1	19970401	AU 1996-70181 19960911
AU 703101	B2	19990318	
EP 859631	A1	19980826	EP 1996-931527 19960911
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI			
JP 11514985	T2	19991221	JP 1996-512063 19960911
ZA 9607757	A	19970407	ZA 1996-7757 19960913
US 6136315	A	20001024	US 1998-150204 19980909
US 6139841	A	20001031	US 1998-150039 19980909
US 6143299	A	20001107	US 1998-150203 19980909
US 6162436	A	20001219	US 1998-150041 19980909
US 6187312	B1	20010213	US 1998-150040 19980909
PRIORITY APPLN. INFO.:			US 1995-527391 A 19950913
			WO 1996-US14557 W 19960911

AB Methods and compns. are disclosed for eliciting an immune response and the prevention and treatment of primary and metastatic neoplastic diseases and infectious diseases. The methods comprise administering a compn. comprising an effective amt. of a complex, in which the complex consists essentially of a **heat shock protein** (**hsp**) noncovalently bound to an antigenic mol. "Antigenic mol." refers to the **peptides** with which the **hsps** are endogenously assocd. in vivo as well as exogenous **antigens**/immunogens (i.e., with which the **hsps** are not complexed in vivo or antigenic/immunogenic fragments and derivs. thereof). In a preferred embodiment, the complex is autologous to the individual. The effective amts. of the complex are in the range of 100-600 .mu.g for complexes comprising **hsp70**, 50-1000 .mu.g for **hsp90**, and 10-600 .mu.g for gp96. The invention also provides a method for measuring tumor rejection in vivo in an individual, preferably a human, comprising a measuring the generation by the individual of MHC Class I-restricted **CD8** + **cytotoxic T-lymphocytes** specific to the tumor. Methods of purifying **hsp70-peptide** complexes are also provided. Administration of gp96 prepns. derived from UV-induced carcinomas immunized syngeneic mice from the resp. cancer cell type.

L6 ANSWER 18 OF 22 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER:	1997:87993 HCAPLUS
DOCUMENT NUMBER:	126:143052
TITLE:	Synthetic **peptides** based on Chlamydia trachomatis **antigens** identify cytotoxic T lymphocyte responses in subjects from a trachoma-endemic population
AUTHOR(S):	Holland, M. J.; Conway, D. J.; Blanchard, T. J.; Mahdi, O. M. S.; Bailey, R. L.; Whittle, H. C.; Mabey, D. C. W.
CORPORATE SOURCE:	Department of Clinical Sciences, London School

of Hygiene and Tropical Medicine, London, UK
SOURCE: Clinical and Experimental Immunology (1997), 107(1), 44-49
CODEN: CEXIAL; ISSN: 0009-9104
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **CD8+ cytotoxic T lymphocytes** (CTL) recognize **peptide antigens** in the context of class I MHC **antigen** mols. To identify **peptides** capable of eliciting anti-Chlamydia trachomatis CTL responses, 13 synthetic **peptides** conforming to human leukocyte **antigen** (HLA)-B8- or -B35-predicted binding motifs were synthesized using sequences based on C. trachomatis major outer membrane **protein** (MOMP) and **heat shock protein** 60 (hsp60). Two of 11 HLA-B35-predicted binding **peptides** were able to stabilize HLA-B35 in an in vitro binding assay. All **peptides** were tested in CTL assays using peripheral blood mononuclear cells (PBMC) isolated from 26 HLA-B8 or -B35 individuals resident in a trachoma-endemic community. Responses to MOMP and hsp60 **peptides** were identified in a minority of both HLA-B8 and -B35 individuals. Two of 12 HLA-B8 subjects responded to MOMP and 1/13 to hsp60 **peptides**. Responses in HLA-B35 subjects were similar, 1/13 subjects responding to MOMP and 2/13 to hsp60 **peptides**. CTL responses were obsd. only in children resolving current infection and in adults without scarring of the conjunctiva. These results suggest that anti-chlamydial CTL occur at low levels in peripheral blood, but may be important in the resoln. of naturally acquired human ocular chlamydial infection.

L6 ANSWER 19 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:271414 HCAPLUS
DOCUMENT NUMBER: 122:53505
TITLE: Elongated **peptides**, not the predicted nonapeptide stimulate a major histocompatibility complex class I-restricted cytotoxic T lymphocyte clone with specificity for a bacterial **heat shock protein**
AUTHOR(S): Schoel, Bernd; Zuegel, Ulrich; Ruppert, Thomas; Kaufmann, Stefan H. E.
CORPORATE SOURCE: Dep. Immunology, Univ. Ulm, Ulm, Germany
SOURCE: European Journal of Immunology (1994), 24(12), 3161-9
CODEN: EJIMAF; ISSN: 0014-2980
PUBLISHER: VCH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **peptides** recognized by an H-2Db-restricted **CD8 cytotoxic T lymphocyte** (CTL) clone which is specific for the 60-kDa mycobacterial **heat shock protein** (**hsp**) and cross-reacts with stressed host cells were characterized. None of the nonapeptides from hsp60 conforming to the H-2Db binding motif were able to sensitize target cells for lysis by this CTL clone. Sequence anal. of the stimulatory fraction from a trypsin digest of hsp60, together with synthetic **peptide** studies, defined a

cluster of overlapping epitopes. C-terminal extension by at least one amino acid of the nonamer predicted to bind best to H-2Db was essential for CTL recognition. Two such elongated **peptides**, a 10-mer and a 12-mer stimulated the clone at similarity low concns. in the 100 pM range. The authors assume that these two **peptides** comply best with the natural epitope. In contrast, the 11-mer was inactive. The stimulatory 10-mer bound to H-2Db with an efficacy similar to that of the nonapeptide corresponding to the H-2Db motif, as revealed by **peptide** induced major histocompatibility complex (MHC) surface expression on RMA-S cells and competitive blocking of epitope recognition by the nonamer. Binding of these C-terminally extended **peptides** to the MHC groove can be explained by anchoring through the amino acid residue Asn in position 5 of the **peptide** and by intrusion of the hydrophobic C-terminal Ala(10-mer) or Leu(12-mer), but not Gly(11-mer), into the hydrophobic pocket of the H-2Db cleft. Because the C-terminal part is thus larger than predicted, this region of the **peptide** may arch up from the binding groove. The authors assume that recognition of steric components of the MHC/**peptide** complex broaden the range of epitope specificity for a single T cell receptor. This flexibility not only promotes recognition of several overlapping **peptides** from a single **antigen**, but may also increase the change of cross-reaction with similar **peptides** from unrelated **proteins**, including autoantigens. Consistent with this latter assumption, the T cell clone cross-recognizes mycobacterial hsp60 and stressed host cells.

L6 ANSWER 20 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:678399 HCAPLUS
DOCUMENT NUMBER: 121:278399
TITLE: .beta.2-microglobulin independent presentation of exogenously added foreign **peptide** and endogenous self-epitope by MHC class I .alpha.-chain to a cross-reactive **CD8+** **CTL** clone
AUTHOR(S): Zugel, Ulrich; Schoel, Bernd; Kaufmann, Stefan H. E.
CORPORATE SOURCE: Dep. Immunology, Univ. Ulm, Ulm, Germany
SOURCE: Journal of Immunology (1994), 153(9), 4070-80
CODEN: JOIMA3; ISSN: 0022-1767
DOCUMENT TYPE: Journal
LANGUAGE: English
AB CD8+ T cells recognize antigenic **peptides** in the context of MHC class I mols. that encompass two distinct **polypeptide** chains, the MHC-encoded .alpha.-chain and the non-MHC-encoded .beta.2-microglobulin (.beta.2-m). The .beta.2-m is considered essential for the stability and function of the MHC class I **peptide** complex and, hence, for **peptide** presentation to CD8+ T cells. In this study, we describe **peptide** presentation by macrophages from .beta.2-m-deficient mice to a **CD8+** **CTL** clone that cross-recognizes an H-2Db-restricted **peptide** of the mycobacterial **heat shock protein** 60 (hsp60) and a self-**peptide** presented by IFN-.gamma.-stressed macrophages. Specific lysis of stressed or hsp60 **peptide** -pulsed .beta.2-m-/- macrophages was inhibited by the nucleoprotein **peptide** with high affinity to H-2Db. Brefeldin A, a known

inhibitor of MHC class I processing, interfered with lysis of IFN-.gamma.-stressed, but not of hsp60 **peptide**-pulsed, .beta.2-m-/- macrophages. The hsp60 **peptide** failed to stimulate surface expression of H-2Db in .beta.2-m-/- macrophages, and slightly increased MHC class I expression in the transporter mutant cell line RMA-S, as detected by cytofluorometry. We conclude that presentation of endogenously processed cytosolic epitopes and exogenously added foreign **peptides** by the MHC class I .alpha.-chain can occur independent from .beta.2-m. Presumably, H-2Db **peptides**, but not H-2Kb **peptides**, have the capacity to induce and/or stabilize surface expression of a small no. of MHC class I .alpha.-chains, and this low d. is sufficient for recognition by **CD8+ CTL**, although it need not be detected by serol. means.

L6 ANSWER 21 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:58080 HCAPLUS
DOCUMENT NUMBER: 118:58080
TITLE: Autoreactive and **heat shock protein** 60-recognizing CD4+ T-cells show antitumor activity against syngeneic fibrosarcoma
AUTHOR(S): Harada, Mamoru; Matsuzaki, Goro; Yoshikai, Yasunobu; Kobayashi, Noritada; Kurosawa, Shin; Takimoto, Hiroaki; Nomoto, Kikuo
CORPORATE SOURCE: Med. Inst. Bioregul., Kyushu Univ., Fukuoka, 812, Japan
SOURCE: Cancer Research (1993), 53(1), 106-11
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A CD4+ **heat shock protein** (**hsp**) 60-recognizing autoreactive T-cell line (BASL1) and clone (BASL1.1) were examd. for their antitumor activity against major histocompatibility complex class II- syngeneic Meth A fibrosarcoma (Meth A), which was immunofluorescently stained with monoclonal antibody specific for **hsp** 60. In an in vitro proliferative assay, BASL1.1 apparently recognized Meth A-derived **hsp** 60 presented by syngeneic **antigen**-presenting cells in a major histocompatibility complex class II-restricted manner. This cell line and clone showed antitumor activity in a tumor-neutralizing (Winn) assay. BASL1 and BASL1.1 cells produced .gamma.-interferon, tumor necrosis factor, and interleukin 2 but not interleukin 4 by stimulation with syngeneic spleen cells. In cytolytic assay, these cell lines and clones showed neither direct nor indirect (bystander) cytolysis of Meth A. In cytostatic assay, these cells inhibited the proliferation of Meth A in the presence of syngeneic macrophages, and this activity was abrogated by the addn. of anti-.gamma.-interferon monoclonal antibody. Recombinant .gamma.-interferon could induce cytostatic activity only in the presence of macrophages, and tumor necrosis factor synergized this activity. Antitumor activity induced by BASL1 was abrogated by the administration of anti-CD8 monoclonal antibody in vivo, suggesting that **CD8+ cytotoxic T-lymphocytes** are essential and final effector cells for BASL1-mediated Meth A rejection. Thus, CD4+ autoreactive and **hsp** 60-recognizing T-cells show 2 types of antitumor activity: cytostasis and induction of tumor-specific cytotoxic

T-lymphocytes. Furthermore, these results imply that tumor-specific immunity could be elicited by CD4+ helper T-cells which recognize **hsp**.

L6 ANSWER 22 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:476061 HCAPLUS
DOCUMENT NUMBER: 113:76061
TITLE: Specific killing of cytotoxic T cells and **antigen**-presenting cells by CD4+ cytotoxic T cell clones. A novel potentially immunoregulatory T-T cell interaction in man
AUTHOR(S): Ottenhoff, Tom H. M.; Mutis, Tuna
CORPORATE SOURCE: Dep. Immunohaematol., Univ. Hosp., Leiden, 2300 RC, Neth.
SOURCE: Journal of Experimental Medicine (1990), 171(6), 2011-24
CODEN: JEMEAV; ISSN: 0022-1007
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The mycobacterial recombinant 650kD **heat shock protein** (**hsp**) was previously found to be an important target **antigen** for polyclonal CD4+ CTL. Because of the major role of 65-kD **hsp** in the immune response to mycobacterial as well as autoantigens, CTL activity to this **protein** was studied at the clonal level. HLA-DR or HLA-DQ restricted, CD4+CD8-T cell clones that recognize different **peptides** of the M. leprae 65-kD **hsp** strongly lysed EBV-BLCL pulsed with specific but not irrelevant **peptide**. No bystander lysis of B cells, T cells, or tumor cells was seen. Target cell lysis could not be triggered by PMA + Ca2+ ionophore alone and depended on active metab. These CD4+ CTL also strongly lysed themselves and other HLA-class II compatible CD4+ (TCR-.alpha./.beta. or -.gamma./.delta.) or **CD8+** **CTL** clones in the presence of **peptide**, suggesting that CTL are not actively protected from CTL-mediated lysis. Cold target competition expts. suggested that EBV-BLCL targets were more efficiently recognized than CD4+ CTL targets. These results demonstrate that **hsp65** **peptide**-specific HLA class II-restricted CD4+ T cell clones display strong **peptide**-dependent cytolytic activity towards both APCs, and, unexpectedly, CD4+ and **CD8+** **CTL** clones, including themselves. Since, in contrast to murine T cells human T cells express class II, CTL-mediated T cell killing may represent a novel immunoregulatory pathway in man.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 09:41:27 ON 07 NOV 2002)
L7 93 S L6
L8 45 DUP REM L7 (48 DUPLICATES REMOVED)

L8 ANSWER 1 OF 45 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2002-619261 [66] WPIDS
DOC. NO. CPI: C2002-175015
TITLE: Nucleic acid molecule encoding a fusion **polypeptide** that promotes processing via the Major Histocompatibility Complex class I pathway and/or promotes activity of an **antigen** presenting cell, useful as vaccine

for cancer and viral infections.
DERWENT CLASS: B04 D16
INVENTOR(S): HUNG, C; WU, T
PATENT ASSIGNEE(S): (UYJO) UNIV JOHNS HOPKINS
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002061113	A2	20020808	(200266)*	EN	127

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002061113	A2	WO 2002-US2598	20020201

PRIORITY APPLN. INFO: US 2001-265334P 20010201
AN 2002-619261 [66] WPIDS
AB WO 200261113 A UPAB: 20021014
NOVELTY - A new nucleic acid molecule (I) encoding a fusion **polypeptide** useful as a vaccine composition, comprising a first nucleic acid sequence encoding a first **polypeptide** or **peptide** that promotes processing via the Major Histocompatibility Complex class I pathway (MHC-I-PP) and/or promotes development or activity of an **antigen** presenting cell (APC), is new.

DETAILED DESCRIPTION - A new nucleic acid molecule (I) encoding a fusion **polypeptide** useful as a vaccine composition, comprising a first nucleic acid sequence encoding a first **polypeptide** or **peptide** that promotes processing via the Major Histocompatibility Complex class I pathway (MHC-I-PP) and/or promotes development or activity of an **antigen** presenting cell (APC). The nucleic acid molecule optionally comprises fused in frame with the first nucleic acid sequence, a linker nucleic acid sequence encoding a linker **peptide**, and a second nucleic acid sequence that is linked in frame to the first nucleic acid sequence or to the linker nucleic acid sequence and that encodes an antigenic **polypeptide** or **peptide**.

INDEPENDENT CLAIMS are also included for the following:

(1) an isolated nucleic acid molecule that under stringent conditions hybridizes simultaneously with at least part of the nucleic acid sequence and at least part of the second, first and/or linker nucleic acid sequence, or at least part of the second nucleic acid sequence and part of the linker nucleic acid sequence;

(2) an expression vector comprising (I) operatively linked to a promoter, and optionally, additional regulatory sequences that regulate expression of the nucleic acid in eukaryotic cell;

(3) a cell which has been modified to comprise (I) or the

expression vector of (2);

(4) a particle comprising (I) or the expression vector of (2);

(5) a fusion or chimeric particle comprising a first **polypeptide** that promotes processing via the MHC class I pathway and/or promotes development or activity of an APC, and a second **polypeptide** comprising an antigenic **peptide** or **polypeptide**;

(6) a pharmaceutical composition capable of inducing or enhancing an **antigen**-specific immune response comprising a pharmacologically or immunologically acceptable excipient in combination with:

(a) the expression vector of (2) and (I);

(b) the cell of (3);

(c) the particle of (4);

(d) the fusion or chimeric **polypeptide** of (5); or

(e) any combination of (a)-(d);

(7) a method of inducing or enhancing an **antigen** specific immune response in cells or in a subject comprising contacting the cells with, or administering to the subject the pharmaceutical composition of (6), therefore inducing or enhancing the response;

(8) a method of increasing the numbers or lytic activity of **CD8+ CTLs** specific for a selected **antigen** comprising administering the pharmaceutical composition of (6), where the nucleic acid molecule, the expression vector, the cell, the particle or the fusion or chimeric **polypeptide** comprises the selected **antigen**, and the selected **antigen** comprises an epitope that binds to, and is presented on the cell surface by, MHC class I **proteins**; and

(9) a method of inhibiting growth or preventing re-growth of a tumor in a subject comprising administering the pharmaceutical composition of (6), where the nucleic acid molecule, the expression vector, the cell, the particle or the fusion or chimeric **polypeptide** comprises one or more tumor-associated or tumor-specific groups present on the tumor, therefore inhibiting the growth or preventing the re-growth.

ACTIVITY - Cytostatic; Virucide.

A Sindbis RNA vaccine linking E7 with **Hsp70** significantly increased expansion and activation of E7-specific CD8+ cells and NK cells, bypassing requirement for CD4+ T cell-mediated help and resulting in potent anti-tumor immunity against E7-expressing tumors. Mechanistic studies confirmed that the Sindbis E7/**Hsp70** RNA vaccine induced apoptotic death of host cells and promoted processing of this apoptotic material by dendritic cells leading to significantly increased expansion and activation of E7-specific CD8+ cells. The enhanced CD8 response resulted in a state of potent anti-tumor immunity against an E7-expressing tumor cell line.

MECHANISM OF ACTION - Gene therapy, CD8-Agonist; Vaccine.

USE - The methods and compositions of the present invention are useful as therapeutic vaccine for cancer and for major viral infections, such as hepatoma and cervical cancer, that cause morbidity and mortality. They can also be used in treating animal diseases, such as equine herpesvirus, bovine viruses, Marek's disease, retroviral and lentiviral diseases and rabies, in the veterinary medicine context.

Dwg.0/26

L8 ANSWER 2 OF 45 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:370904 BIOSIS
DOCUMENT NUMBER: PREV200200370904
TITLE: Dendritic cells can directly acquire the NY-ESO-1 tumor **antigen** and cross-present to CTL.
AUTHOR(S): Zeng, Gang (1); Robbins, Paul F. (1); Rosenberg, Steven A. (1)
CORPORATE SOURCE: (1) Surgery Branch, National Cancer Institute, Bldg10, Rm4B50, Bethesda, MD, 20892 USA
SOURCE: FASEB Journal, (March 22, 2002) Vol. 16, No. 5, pp. A1232. http://www.fasebj.org/. print.
Meeting Info.: Annual Meeting of Professional Research Scientists on Experimental Biology New Orleans, Louisiana, USA April 20-24, 2002
ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB "Cross-priming" plays an important role in generating **CD8+ Cytotoxic T Lymphocytes** (CTL) against tumor and viral **antigens** in vivo. **Antigens** present in apoptotic bodies, complexed with IgG, or chaperoned by **heat shock proteins** can be acquired by professional **antigen** presenting cells (APC) and cross-presented to **CD8+ CTL**. We report that dendritic cells (DC) can directly acquire exogenous NY-ESO-1 tumor **antigen protein** and cross-present to **CD8 + CTLs**. Both the HLA-A2 and A31-restricted epitopes, ESO p157-165 and ESO p53-62 were efficiently cross-presented to respective CTL clones. Efficient cross-presentation requires the full-length but not the truncated form of the **protein**; and only DC but not CD40 ligand activated B lymphocytes or fiboblasts are capable of cross-presentation. Further studies indicate that the full-length NY-ESO-1 **protein** is efficiently ingested to an endosome/lysosome compartment of DC through interactions with DC cell surface. Cross-priming through direct **antigen**-APC interactions may indicate a different pathway from the above-described cross-priming routes. The cross-priming ability of the NY-ESO-1 **protein** may also provide an explanation for the unusual immunogenicity of NY-ESO-1 and its ability to stimulate CD4+ and CD8+ T cell responses as well as antibody responses in cancer patients.

L8 ANSWER 3 OF 45 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:353898 BIOSIS
DOCUMENT NUMBER: PREV200200353898
TITLE: Secreted gp96-ig mediates CD8 and NK cell expansion.
AUTHOR(S): Strbo, Natasa (1); Zimmerman, Zach (1); Koichi, Yamazaki (1); Nguyen, Timmy (1); Podack, Eckhard R.
CORPORATE SOURCE: (1) Microbiology, Medical School, University of Miami, 1600 NW 10th Ave, RMSB 3008, Miami, FL, 33101 USA
SOURCE: FASEB Journal, (March 20, 2002) Vol. 16, No. 4, pp. A336. http://www.fasebj.org/. print.
Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology New Orleans, Louisiana, USA April 20-24, 2002
ISSN: 0892-6638.
DOCUMENT TYPE: Conference

LANGUAGE: English

AB **Heat shock protein (HSP)** gp96 is a major component in the lumen of the endoplasmatic reticulum (ER). We developed a secretory form of gp96 by deleting KDEL sequence and replacing it with the hinge, CH2 and CH3 domains of murine IgG1. Transfection of tumor cell line EG7 with cDNA for gp96-Ig resulted in gp96-Ig secretion. Our aim was to determine the cellular and molecular mechanisms of the **CD8 CTL** response to secreted gp96-Ig in vivo. We utilized the TCR transgenic adoptive transfer system: 1 million TCR transgenic CD8 cells (OT1) specific for ovalbumin derived **peptide** SIINFEKL presented by Kb were transferred into syngeneic (C57B1/6) mice. After two days mice were immunized with 1 million of EG7-gp96-Ig (tumor secreted gp96-Ig). We found out that OT1 expansion takes place within the first seven days (increasing from less than 1% to 20% of CD8 cells) and then returns to lower frequency by day 14. Secreted gp96-Ig mediates NK expansion during the first three days followed by **CD8 CTL** expansion. Further, when we depleted NK cells from wild type C57B1/6 mice with anti asialo-GM2, OT1 did not expand as seen in normally wild type mice but was drastically diminished to 3% after 7 days. We are reporting expansion of classical NK cell (up to 10% frequency after two days) as well as NKT cell expansion upon EG7-gp96-Ig vaccination. In conclusion: we have shown that in vivo engagement of NK and NKT cells by EG7gp96-Ig rapidly induces expansion of CTL CD8 cells.

L8 ANSWER 4 OF 45 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 1

ACCESSION NUMBER: 2002:560359 BIOSIS
DOCUMENT NUMBER: PREV200200560359
TITLE: Heat shock fusion **protein** gp96-Ig mediates strong **CD8 CTL** expansion in vivo.
AUTHOR(S): Strbo, Natasa; Yamazaki, Koichi; Lee, Kelvin; Rukavina, Daniel; Podack, Eckhard R. (1)
CORPORATE SOURCE: (1) Department of Microbiology and Immunology, 1600 NW 10th Avenue, RMSB 3045 (R-138), Miami, FL, 33136: epodack@miami.edu USA
SOURCE: American Journal of Reproductive Immunology, (October, 2002) Vol. 48, No. 4, pp. 220-225. http://www.blackwellmunksgaard.com/ajri. print. ISSN: 1046-7408.
DOCUMENT TYPE: Article
LANGUAGE: English

AB PROBLEM: As shown previously, gp96-Ig **peptide** complexes secreted by an ovalbumin transfected tumor (EG7) mediate strong, specific tumor immunity through a CD4 T cell independent **CD8 + CTL** response. In this study, we set out to develop a system to quantitatively determine the **CD8 CTL** response to gp96-Ig and to evaluate the influence of an established wild type tumor. METHODS: Secreted **heat shock protein** gp96-Ig was constructed by replacement of the endoplasmic reticulum retention signal with the Fc portion of IgG1, transfected into EG7 (EG7-gp96-Ig) and used to induce **CD8+ CTL** expansion in vivo. Adoptively transferred, ovalbumin specific T-cell receptor (TCR) transgenic CD8+ cells (OT-1) responded with clonal expansion to the immunization with EG7-gp96-Ig. OT-1 expansion was quantitated with Kb-**peptide** -tetramers by flow cytometry. RESULTS: In response to primary

immunization with EG7-gp96-Ig, OT-1 expand from an initial frequency of 0.5 to 25% of all CD8 cells, and to 50% of all CD8 cells after a booster immunization. Endogenous ovalbumin specific CD8 cells also expand strongly. **Antigen** specific effector function was measured by enzyme-linked immunosorbent spot-forming cell assay (ELISPOT) for interferon-gamma (IFN-gamma). While effector function was strongly induced by secreted gp96-Ig, not all expanded OT-1 produce IFN-gamma. EG7 does not cause OT-1 expansion, but rather induces anergy. If OT-1 are transferred into wild type EG7 tumor bearing mice to induce anergy of OT-1, immunization with EG7-gp96-Ig can partly overcome unresponsiveness. CONCLUSIONS: We conclude that secreted gp96-Ig is a powerful mediator of specific **CD8+ CTL** responses in vivo. Secretory gp96 mimics release of gp96 by damaged or necrotic cells that is able to activate dendritic cells without CD4 help. Gp96-Ig associated **peptides** have not been selected by binding to major histocompatibility complex (MHC). Specific immunization by secreted gp96-Ig therefore is expected to occur also in allogeneic settings.

L8 ANSWER 5 OF 45 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:350527 BIOSIS
DOCUMENT NUMBER: PREV200100350527
TITLE: Compositions and methods using complexes of **heat shock protein** 90 and antigenic molecules for the treatment and prevention of infectious diseases.
AUTHOR(S): Srivastava, Pramod K.
ASSIGNEE: Fordham University
PATENT INFORMATION: US 6187312 February 13, 2001
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Feb. 13, 2001) Vol. 1243, No. 2, pp. No Pagination. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English

AB The invention relates to methods and compositions for eliciting an immune response and the prevention and treatment of primary and metastatic neoplastic diseases and infectious diseases. The methods of the invention comprise administering a composition comprising an effective amount of a complex, in which the complex consists essentially of a **heat shock protein** (**hsp**) noncovalently bound to an antigenic molecule. "Antigenic molecule" as used herein refers to the **peptides** with which the **hsps** are endogenously associated in vivo as well as exogenous **antigens**/immunogens (i.e., with which the **hsps** are not complexed in vivo) or antigenic/immunogenic fragments and derivatives thereof. In a preferred embodiment, the complex is autologous to the individual. The effective amounts of the complex are in the range of 10-600 micrograms for complexes comprising **hsp70**, 50-1000 micrograms for **hsp90**, and 10-600 micrograms for gp96. The invention also provides a method for measuring tumor rejection in vivo in an individual, preferably a human, comprising measuring the generation by the individual of MHC Class I-restricted **CD8 +cytotoxic T lymphocytes** specific to the tumor. Methods of purifying **hsp70-peptide** complexes are also provided.

L8 ANSWER 6 OF 45 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2001-550132 [61] WPIDS
DOC. NO. CPI: C2001-163771
TITLE: Spray-dried **lipid** microparticle composition useful for introducing therapeutic or biologically active agents into a cell, e.g., the introduction of an agent to suppress pathogenic T cells.
DERWENT CLASS: A96 B02 B03 B04 D16
INVENTOR(S): BOT, A; DELLAMARY, L; SMITH, D; WOODS, C M
PATENT ASSIGNEE(S): (ALLI-N) ALLIANCE PHARM CORP
COUNTRY COUNT: 94
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001064254	A2	20010907	(200161)*	EN	46
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001041882	A	20010912	(200204)		
US 2002103165	A1	20020801	(200253)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001064254	A2	WO 2001-US6532	20010227
AU 2001041882	A	AU 2001-41882	20010227
US 2002103165	A1	US 2000-515359	20000229

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001041882	A Based on	WO 200164254

PRIORITY APPLN. INFO: US 2000-515359 20000229
AN 2001-550132 [61] WPIDS
AB WO 200164254 A UPAB: 20011024
NOVELTY - A Spray-Dried **Lipid** Microparticle (SDLM) composition (I), comprising one or more phospholipids, a therapeutic or biologically active agent, and at least one ligand that binds to a cell surface receptor is new
ACTIVITY - Cytostatic; antirheumatic; antiarthritic; antidiabetic; neuroprotective; immunomodulatory.
No supporting data given.
MECHANISM OF ACTION - Class I or Class II major histocompatibility complex (MHC) immune response inducer; activity of T suppressor cells enhancer; activity of pathogenic T cells suppressor; production of suppressor cytokines by **antigen** presenting cells, inducer; gene therapy.
Airway **antigen** presenting cell (APC) were isolated from BALB/c mice by standard bronchoalveolar lavage using normal

phosphate buffered saline (PBS). The recovered cells were washed with 4 deg. C-cold cell culture medium (HL-1) twice and incubated in 96-well flat-bottom plates (1 multiply 105 cells/well) with various amounts of dried-SDLM, corresponding to defined quantities of viral **antigen**. After 1 hour incubation at 37 deg. C under mild horizontal shaking conditions (30 rpm), the non-adherent cells and **lipid** debris were washed off by repeated, gentle addition and removal of HL-1 medium. T cell hybridoma (16-2-6) specific for HA 110-120 epitope of WSN virus were added to the plastic-adherent cells (multiply 104 TcH/well in 100 micro l of HL-1 medium). After 12-hour incubation at 37 deg. C and 5% CO2, the cells were fixed with glutaraldehyde/formaldehyde and X-gal substrate was added. The results showed that addition of a ligand to SDLM improved the efficiency of **antigen** presentation by bronchoalveolar phagocytes, as compared to non-ligand engineered SDLM with **antigen**.

USE - (I) is useful for introducing a therapeutic or biologically active agent into a cell of a subject, where the ligand (an immunoglobulin such as IgG, IgM, IgA, IgE or IgD) and the agent are coupled such that upon binding of the ligand to the cell surface receptor, a ligand-agent-receptor complex is formed and subsequently internalized by the cell, thereby resulting in introduction of the agent into the cell e.g., a macrophage or any **antigen** presenting cell (APC). The method is preferably useful for introducing an **antigen** which upon internalization induces a Class I major histocompatibility complex (MHC) (**CD8+ cytotoxic T lymphocyte** (CTL)) response or Class II MHC response immune response in the subject. The introduction of the agent alternately results in suppression of pathogenic T cells (all claimed).

(I) is also useful for selectively inhibiting or killing the growth of neoplastic cells. The methods to suppress activity of pathogenic T cells can be employed to treat autoimmune diseases e.g., Type I diabetes, multiple sclerosis, rheumatoid arthritis, etc. (I) is also employed for DNA immunization methods, and for introducing therapeutic genes for gene therapy techniques.

ADVANTAGE - (I) is biocompatible and is targetable to a internalizable cell surface receptor. Use of (I) allows improved and effective immune response to be induced against the infectious agents.

Dwg.0/12

L8 ANSWER 7 OF 45 WPIDS (C) 2002 THOMSON DERWENT

ACCESSION NUMBER: 2001-451815 [48] WPIDS

DOC. NO. CPI: C2001-136485

TITLE: Inducing a **CD8+ cytotoxic T lymphocyte** immune response in an individual for treating diseases such as HIV involves administering a fusion molecule comprising a **heat shock protein**.

DERWENT CLASS: B04 D16

INVENTOR(S): CHEN, J; CHO, B K; EISEN, H N; HUANG, Q; PALLISER, D; RICHMOND, J F L; YOUNG, R A

PATENT ASSIGNEE(S): (MASI) MASSACHUSETTS INST TECHNOLOGY; (WHED) WHITEHEAD INST BIOMEDICAL RES

COUNTRY COUNT: 94

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001051081	A1	20010719	(200148)*	EN	58

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2001018141	A	20010724	(200166)	
US 2002146426	A1	20021010	(200269)	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001051081	A1	WO 2000-US32831	20001201
AU 2001018141	A	AU 2001-18141	20001201
US 2002146426	A1 Provisional	US 2000-176143P	20000114
	Cont of	WO 2000-US32831	20001201
		US 2001-761534	20010116

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001018141	A Based on	WO 200151081

PRIORITY APPLN. INFO: US 2000-176143P 20000114; US 2001-761534 20010116

AN 2001-451815 [48] WPIDS

AB WO 200151081 A UPAB: 20010829

NOVELTY - Inducing a **CD8+ cytotoxic T lymphocyte** (CTL) response to a molecule in an individual by administrating a fusion molecule joined to a **heat shock protein** (**hsp**) (I), or an adenosine triphosphate (ATP) binding domain of (I), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a method of inducing a CD4+-independent CTL response to a molecule in an individual comprising administering to the individual a portion of an ATP binding domain of (I) joined to the molecule; and

(2) a composition comprising (I), or a portion joined to a heterologous molecule.

ACTIVITY - Immunostimulant.

MECHANISM OF ACTION - **CD8+ cytotoxic T lymphocyte** inducer. CD4 knockout mice (CD4-/-) were immunized and their ability to produce SYRGL-specific CTL was assessed. The CD4-/- mice produced a CTL response to **hsp65** -P1. No response was elicited to the control Mal-P1.

USE - The method is useful for treating diseases that are caused by or associated with intracellular pathogens. The method is particularly useful for treating diseases that are characterized by a deficiency , or lack of CD4+ T cells, such as acquired immunodefficiency syndrome.

Dwg.0/14

L8 ANSWER 8 OF 45 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001503906 MEDLINE
DOCUMENT NUMBER: 21437670 PubMed ID: 11553607
TITLE: DNA immunization with Trypanosoma cruzi **HSP70** fused to the KMP11 **protein** elicits a cytotoxic and humoral immune response against the **antigen** and leads to protection.
AUTHOR: Planelles L; Thomas M C; Alonso C; Lopez M C
CORPORATE SOURCE: Departamento de Biologia Molecular, Instituto de Parasitologia y Biomedicina Lopez Neyra, CSIC, 18001 Granada, Spain.
SOURCE: INFECTION AND IMMUNITY, (2001 Oct) 69 (10) 6558-63. Journal code: 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20010913
Last Updated on STN: 20011029
Entered Medline: 20011025

AB Murine immunization with Trypanosoma cruzi KMP11-**HSP70** fused genes but not the KMP11 gene alone elicited both an immunoglobulin G2a long-lasting humoral immune response against KMP11 **protein** and activation of **CD8+ cytotoxic T lymphocytes** specific for two KMP11 **peptides** containing A2 motifs. Moreover, protection against the parasite challenge was observed after immunization with the chimeric gene.

L8 ANSWER 9 OF 45 MEDLINE
ACCESSION NUMBER: 2001406636 MEDLINE
DOCUMENT NUMBER: 21351511 PubMed ID: 11457557
TITLE: Protective CTL response is induced in the absence of CD4+ T cells and IFN-gamma by gene gun DNA vaccination with a minigene encoding a CTL epitope of Listeria monocytogenes.
AUTHOR: Yoshida A; Nagata T; Uchijima M; Koide Y
CORPORATE SOURCE: Department of Microbiology and Immunology, Hamamatsu University School of Medicine, 431-3192, Hamamatsu, Japan.
SOURCE: VACCINE, (2001 Jul 20) 19 (30) 4297-306. Journal code: 8406899. ISSN: 0264-410X.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20011001
Last Updated on STN: 20011001
Entered Medline: 20010927

AB Our work was undertaken to learn the mechanism of induction of protective cytotoxic T lymphocytes (CTL) by gene gun DNA vaccination with p91m encoding an H-2Kd-restricted T cell epitope of listeriolysin O (LLO). Vaccination with p91m induced vigorous **antigen**-specific **CD8+ CTL** that produce IFN-gamma and was able to confer partial protection against

listerial challenge. However, the p91m-induced protective immunity was revealed to be independent of the IFN-gamma and CD4+ T cell help. The CTL induction is also suggested to require neither adjuvant activity of the plasmid used nor IFN-gamma. The data may be feasible for the design of CTL inducing vaccines in various immunodeficiencies.

L8 ANSWER 10 OF 45 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 3
ACCESSION NUMBER: 2002:179478 BIOSIS
DOCUMENT NUMBER: PREV200200179478
TITLE: The involvement of class Ib molecules in the host response to infection with Salmonella and its relevance to autoimmunity.
AUTHOR(S): Soloski, Mark J. (1); Metcalf, Eleanor S.
CORPORATE SOURCE: (1) Division of Rheumatology, Department of Medicine and The Graduate Program in Immunology, The Johns Hopkins University School of Medicine, Baltimore, MD, 21218: mski@jhmi.edu USA
SOURCE: Microbes and Infection, (November December, 2001) Vol. 3, No. 14-15, pp. 1249-1259. print.
ISSN: 1286-4579.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Class I molecules with limited polymorphism have been implicated in the host response to infectious agents. Following infection with Salmonella typhimurium, mice develop a **CD8+ CTL** response that specifically recognizes bacteria infected cells. An immunodominant component of the CTL response recognizes a **peptide** epitope derived from the Salmonella GroEL molecule that is presented by the non-polymorphic MHC class Ib molecule Qa-1. T cells recognizing the bacterial **peptide** also cross-recognize a homologous **peptide** from the mammalian hsp60 molecule. Since Qa-1 has a functional equivalent in humans, this observation may be relevant not only to the host response involved in clearing infection but also in understanding the link between infection with Gram-negative pathogens and autoimmune disease.

L8 ANSWER 11 OF 45 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:314826 BIOSIS
DOCUMENT NUMBER: PREV200100314826
TITLE: Priming of HBV core **antigen**-specific CTL activity by immunization with a HBcAg-**heat shock protein** fusion **protein**.
AUTHOR(S): Liu, Hongwei (1); Anthony, Lawrence S. D. (1); Rowse, Gerald J. (1); Recktenwald, Achim (1); Siegel, Marvin I. (1); Mizzen, Lee A. (1)
CORPORATE SOURCE: (1) StressGen Biotechnologies Corp., 350-4243 Glanford Avenue, Victoria, British Columbia, V8Z 4B9 Canada
SOURCE: FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A1006. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001

ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB In humans, recovery from acute infection with hepatitis B virus (HBV) is associated with development of a strong, multi-specific T lymphocyte response directed against a variety of HBV **antigens**. In particular, **CD8+ CTL** activity is believed to be critical in the resolution of acute disease, possibly through non-cytopathic, cytokine-mediated mechanisms. In marked contrast, individuals suffering from chronic type B hepatitis exhibit a weak and narrowly focused T cell response. Successful therapy of chronic HBV infection may depend, at least in part, upon priming of an effective CTL response. We have engineered a chimeric plasmid encoding sequences from the core **antigen** of HBV (HBc) fused to the 5' end of the 65 kDa **heat shock protein** (**Hsp**) gene from Mycobacterium bovis BCG. Recombinant **Hsp65**-HBc fusion **protein** was expressed in E. coli and purified to >90%-homogeneity. Endotoxin analysis indicated the presence of <0.05 EU/mug **protein** in the final product. Mice were immunized subcutaneously with fusion **protein** in the absence of additional adjuvant. Immune spleen cells were restimulated in vitro with known HBc-derived CTL epitope **peptides**. Effector cells were assayed against either **peptide**-pulsed target cells or HBc-transfected target cells in a standard 4 h 51Cr release assay. Lysis of target cells by effector CTL from mice given a single immunization of **Hsp65**-HBc was as high as 60-80%. **Hsp65**-HBc priming of CTL activity was effective in mice of both H-2b and H-2d haplotypes, and two different H-2d mouse strains responded similarly. In contrast, immunization with HBc alone was less effective than **Hsp65**-HBc in priming CTL activity. The results of these studies clearly demonstrate the potential efficacy of **Hsp65**-HBc in the immunotherapy of chronic HBV infection.

L8 ANSWER 12 OF 45 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:275626 BIOSIS
DOCUMENT NUMBER: PREV200100275626
TITLE: Dramatic in vivo expansion of cognate TCR transgenic T-cells during secreted-heat sock **protein** vaccination.
AUTHOR(S): Strbo, Natasa (1); Nguyen, Timmy (1); Podack, Eckhard (1)
CORPORATE SOURCE: (1) Univ. of Miami dept of microbiology, University of Miami School of Medicine, R-138, Miami, FL, 33101 USA
SOURCE: FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A660. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Recently, a novel method of identifying **antigen**-specific T

lymphocytes has been described. Tetrameric MHC-**peptide** complexes have been shown to bind stably and specifically to appropriate MHC-**peptide**-specific T cells receptors. This technique may be used both to quantify and to characterize **antigen**-specific T cells directly. We have exploited this technique to study **antigen**-specific T cells upon immunization with a tumor cell line, EG7, transfected with the heat shock fusion **protein** gp96-Ig (EG7-gp96-Ig). **Peptides** associated with secreted gp96-Ig are transferred to **antigen** presenting cells and presented by class I MHC and stimulate a specific **CD8+ CTL** response causing tumor rejection. The aim of this study was to investigate effects of the secreted **heat shock protein** gp96-Ig on **CD8+CTL** expansion in vivo. B6, PKO, cdd, gld and CD30L KO mice recived 1 million OT1 cells i.v. (OT1 cells are TCR transgenic CD8 cells recognizing the ovalbumin derived **peptide** SIINFEKL presented by Kb). OT1 were specifically detected and quantitated by FACS with the Kb-tetramer associated with SIINFEKL and by ELISPOT assays for IFN-gamma. Prior to injection OT1 cells were stained with CSFE. Mice were immunized with 1 million of EG7-gp96-Ig. We found out that OT1 expansion takes place within the first seven days (increasing from less than 1% to almost 20% of the CD8 cells) and then returns to lower levels by day 14 in B6 mice. Boosting with an additional million EG7-gp96-Ig results in a second dramatic expansion of OT1. Expansion of perforin sufficient OT1 cells does not take place in perforin deficient animals (PKO and cdd) where OT1 cells remain in the 1% range. The expansion of OT1 cells in vivo in response to EG7-gp96-Ig indicates that the secretion of gp96-Ig in association with ovalbumin derived **peptides** is a strong immune stimulus responsible for breaking of tolerance to the tumor in perforin sufficient mice.

L8 ANSWER 13 OF 45 MEDLINE DUPLICATE 4

ACCESSION NUMBER: 2001160221 MEDLINE
DOCUMENT NUMBER: 21159883 PubMed ID: 11260328
TITLE: The ability of heat-killed Mycobacterium vaccae to stimulate a cytotoxic T-cell response to an unrelated **protein** is associated with a 65 kilodalton **heat-shock protein.**
AUTHOR: Skinner M A; Prestidge R; Yuan S; Strabala T J; Tan P L
CORPORATE SOURCE: Genesis Research and Development Corporation Ltd, Auckland, New Zealand.
SOURCE: IMMUNOLOGY, (2001 Feb) 102 (2) 225-33.
Journal code: 0374672. ISSN: 0019-2805.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010410
Last Updated on STN: 20010410
Entered Medline: 20010405

AB Exogenous **antigens** are generally presented by Class II major histocompatibility (MHC) molecules. When administered with an adjuvant, however, they are capable of inducing a CD8+ T-cell response where **antigen** recognition is associated with Class I MHC. Accordingly, immunization with soluble ovalbumin (OVA)

alone does not activate CD8+ cytotoxic T cells (CTL) but when given in complete Freund's adjuvant (CFA), or in formulations of a number of novel adjuvants, an OVA-specific **CD8+ CTL** response can be detected. We show in this report that immunization with soluble OVA mixed with heat-killed Mycobacterium vaccae, but not with other common pathogenic and saprophytic mycobacteria, can activate OVA-specific **CD8+ CTL**. An OVA-specific CTL response is detected when mice are immunized by either the intraperitoneal or intranasal route and their spleen cells are re-stimulated in vitro. Adjuvant activity of heat-killed M. vaccae is present in M. vaccae culture filtrate, in soluble **protein** components of whole M. vaccae and in the 65 kDa **heat-shock protein** (**hsp**) of M. vaccae. Mycobacterium vaccae has previously been shown to have no adverse side-effects in humans. The current results suggest that M. vaccae may be useful as an adjuvant for vaccines and other immunotherapies where **CD8+ CTL** responses to exogenous **proteins** are crucial.

L8 ANSWER 14 OF 45 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2001:592239 SCISEARCH
THE GENUINE ARTICLE: 453UZ
TITLE: Dendritic cells resurrect **antigens** from dead cells
AUTHOR: Larsson M; Fonteneau J F; Bhardwaj N (Reprint)
CORPORATE SOURCE: Rockefeller Univ, 1230 York Ave, New York, NY 10021 USA (Reprint); Rockefeller Univ, New York, NY 10021 USA
COUNTRY OF AUTHOR: USA
SOURCE: TRENDS IN IMMUNOLOGY, (MAR 2001) Vol. 22, No. 3, pp. 141-148.
Publisher: ELSEVIER SCI LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, OXON, ENGLAND.
ISSN: 1471-4906.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 66
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Antigens** that do not normally access the cytoplasm of **antigen**-presenting cells, such as certain tumor and viral **antigens**, become targets of cytotoxic T lymphocytes (CTLs), Over the past 25 years, substantial evidence has emerged for an 'exogenous' pathway for loading MHC class I molecules. Dendritic cells are potent stimulators of T-cell responses and can induce **CD8**(+) **CTLs** by phagocytosis of dead tumor or virus-infected cells. Here, Marie Larsson and colleagues discuss the role of dendritic cells in stimulating MHC class I-restricted T-cell responses by exogenous routes.

L8 ANSWER 15 OF 45 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2001206660 MEDLINE
DOCUMENT NUMBER: 21144513 PubMed ID: 11249728
TITLE: Unraveling the mechanisms by which **heat shock proteins** activate the immune system.
AUTHOR: Palliser D
CORPORATE SOURCE: Center for Cancer Research and Department of Biology, Massachusetts Institute of Technology, Cambridge, MA

02139, USA.. dpp60@mit.edu
SOURCE: Curr Opin Mol Ther, (2001 Feb) 3 (1) 25-30. Ref: 37
Journal code: 100891485. ISSN: 1464-8431.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010417
Last Updated on STN: 20010417
Entered Medline: 20010412

AB A role for **heat shock proteins** in eliciting **CD8 cytotoxic T-lymphocyte** (CTL) responses in the absence of exogenous adjuvants has been documented for some time. Only recently, however, has the mechanism by which these molecules are able to elicit such responses begun to be elucidated.

L8 ANSWER 16 OF 45 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:294258 BIOSIS
DOCUMENT NUMBER: PREV200100294258
TITLE: Compositions and methods using complexes of **heat shock protein** 90 and antigenic molecules for the treatment and prevention of neoplastic diseases.
AUTHOR(S): Srivastava, Pramod K.
ASSIGNEE: Fordham University
PATENT INFORMATION: US 6162436 December 19, 2000
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Dec. 19, 2000) Vol. 1241, No. 3, pp. No Pagination. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English

AB The present invention relates to methods and compositions for eliciting an immune response and the prevention and treatment of primary and metastatic neoplastic diseases and infectious diseases. The methods of the invention comprise administering a composition comprising an effective amount of a complex, in which the complex consists essentially of a **heat shock protein** (**hsp**) noncovalently bound to an antigenic molecule. "Antigenic molecule" as used herein refers to the **peptides** with which the **hsps** are endogenously associated in vivo as well as exogenous **antigens** /immunogens (i.e., with which the **hsps** are not complexed in vivo) or antigenic/immunogenic fragments and derivatives thereof. In a preferred embodiment, the complex is autologous to the individual. The effective amounts of the complex are in the range of 10-600 micrograms for complexes comprising hsp7o, 50-1000 micrograms for hsp9o, and 10-600 micrograms for gp96. The invention also provides a method for measuring tumor rejection in viva in an individual, preferably a human, comprising measuring the generation by the individual of MHC Class I-restricted **CD8+ cytotoxic T lymphocytes** specific to the tumor. Methods of purifying hsp7o-**peptide** complexes are also provided.

L8 ANSWER 17 OF 45 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:253294 BIOSIS
DOCUMENT NUMBER: PREV200100253294
TITLE: Compositions and methods using complexes of **heat shock protein** gp96 and antigenic molecules for the treatment and prevention of infectious diseases.
AUTHOR(S): Srivastava, Pramod K.
ASSIGNEE: Fordham University
PATENT INFORMATION: US 6143299 November 07, 2000
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Nov. 7, 2000) Vol. 1240, No. 1, pp. No Pagination. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
AB The present invention relates to methods and compositions for eliciting an immune response and the prevention and treatment of primary and metastatic neoplastic diseases and infectious diseases. The methods of the invention comprise administering a composition comprising an effective amount of a complex, in which the complex consists essentially of a **heat shock protein** (**hsp**) noncovalently bound to an antigenic molecule. "Antigenic molecule" as used herein refers to the **peptides** with which the **hsps** are endogenously associated in vivo as well as exogenous **antigens** /immunogens (i.e., with which the **hsps** are not complexed in vivo) or antigenic/immunogenic fragments and derivatives thereof. In a preferred embodiment, the complex is autologous to the individual. The effective amounts of the complex are in the range of 10-600 micrograms for complexes comprising **hsp70**, 50-1000 micrograms for **hsp90**, and 10-600 micrograms for gp96. The invention also provides a method for measuring tumor rejection in vivo in an individual, preferably a human, comprising measuring the generation by the individual of MHC Class I-restricted **CD8** + **cytotoxic T lymphocytes** specific to the tumor. Methods of purifying **hsp70-peptide** complexes are also provided.

L8 ANSWER 18 OF 45 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:253240 BIOSIS
DOCUMENT NUMBER: PREV200100253240
TITLE: Compositions and methods using complexes of **heat shock protein** 70 and antigenic molecules for the treatment and prevention of infectious diseases.
AUTHOR(S): Srivastava, Pramod K.
ASSIGNEE: Fordham University
PATENT INFORMATION: US 6139841 October 31, 2000
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Oct. 31, 2000) Vol. 1239, No. 5, pp. No Pagination. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
AB The present invention relates to methods and compositions for eliciting an immune response and the prevention and treatment of

inhibitors of endosomal acidification (chloroquine, ammonium chloride, and monensin) and by the acid protease inhibitor pepstatin A, suggesting that endocytic processing may play an essential role in CD8 recognition of this Ag. To formally establish that this pattern of exogenous Ag processing requires the presence of a class I MHC product, we demonstrated that beta-2 microglobulin-deficient macrophages, which lack class I MHC product expression, cannot present HKLM to CD8 cells. However, we could not block Ag presentation by incubating macrophages with monoclonal anti-H-2K or H-2D antibodies, suggesting that LM Ag presentation may be mediated by some other class I MHC product. Additional characterization of this pathway of Ag presentation is warranted in view of its possible role in initiating CD8-mediated immunity against microbial Ag.

L8 ANSWER 45 OF 45 MEDLINE DUPLICATE 18
ACCESSION NUMBER: 90278355 MEDLINE
DOCUMENT NUMBER: 90278355 PubMed ID: 1972178
TITLE: Specific killing of cytotoxic T cells and **antigen**-presenting cells by CD4+ cytotoxic T cell clones. A novel potentially immunoregulatory T-T cell interaction in man.
AUTHOR: Ottenhoff T H; Mutis T
CORPORATE SOURCE: Department of Immunohaematology and Blood Bank, University Hospital, Leiden, The Netherlands.
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1990 Jun 1) 171 (6) 2011-24.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199007
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Last Updated on STN: 19950206
Entered Medline: 19900716

AB Mycobacterial **antigens** not only stimulate Th cells that produce macrophage-activating factors, but also CD4+ and **CD8** + **CTL** that lyse human macrophages. The mycobacterial recombinant 65-kD **hsp** was previously found to be an important target **antigen** for polyclonal CD4+ CTL. Because of the major role of 65-kD **hsp** in the immune response to mycobacterial as well as autoantigens, we have studied CTL activity to this **protein** at the clonal level. HLA-DR or HLA-DQ restricted, CD4+CD8- T cell clones that recognize different **peptides** of the M. leprae 65-kD **hsp** strongly lysed EBV-BLCL pulsed with specific but not irrelevant **peptide**. No bystander lysis of B cells, T cells, or tumor cells was seen. Target cell lysis could not be triggered by PMA + Ca2+ ionophore alone and depended on active metabolism. Interestingly, these CD4+ CTL also strongly lysed themselves and other HLA-class II compatible CD4+ (TCR-alpha/beta or -gamma/delta) or **CD8+ CTL** clones in the presence of **peptide**, suggesting that CTL are not actively protected from CTL-mediated lysis. Cold target competition experiments suggested that EBV-BLCL targets were more efficiently recognized than CD4+ CTL targets. These results demonstrate that **hsp65 peptide**-specific HLA class II-restricted CD4+ T cell clones display strong **peptide**-dependent cytolytic activity towards both APCs, and,

unexpectedly, CD4+ and CD8+ CTL clones, including themselves. Since, in contrast to murine T cells human T cells express class II, CTL-mediated T cell killing may represent a novel immunoregulatory pathway in man.

FILE 'MEDLINE' ENTERED AT 09:44:28 ON 07 NOV 2002)

L9	15922	SEA FILE=MEDLINE	ABB=ON	PLU=ON	"T-LYMPHOCYTES, CYTOTOXIC"/CT
L10	10943	SEA FILE=MEDLINE	ABB=ON	PLU=ON	"HEAT-SHOCK PROTEINS"/CT
L11	75	SEA FILE=MEDLINE	ABB=ON	PLU=ON	L9 AND L10
L12	7967	SEA FILE=MEDLINE	ABB=ON	PLU=ON	"CD8-POSITIVE T-LYMPHOCYTES"/CT
L13	6	SEA FILE=MEDLINE	ABB=ON	PLU=ON	L11 AND L12

L9	15922	SEA FILE=MEDLINE	ABB=ON	PLU=ON	"T-LYMPHOCYTES, CYTOTOXIC"/CT
L10	10943	SEA FILE=MEDLINE	ABB=ON	PLU=ON	"HEAT-SHOCK PROTEINS"/CT
L11	75	SEA FILE=MEDLINE	ABB=ON	PLU=ON	L9 AND L10
L14	15802	SEA FILE=MEDLINE	ABB=ON	PLU=ON	"CD4-POSITIVE T-LYMPHOCYTES"/CT
L15	11	SEA FILE=MEDLINE	ABB=ON	PLU=ON	L11 AND L14

L16 15 L13 OR L15

L16 ANSWER 1 OF 15 MEDLINE
AN 2001669022 MEDLINE
TI Two Listeria monocytogenes vaccine vectors that express different molecular forms of human papilloma virus-16 (HPV-16) E7 induce qualitatively different T cell immunity that correlates with their ability to induce regression of established tumors immortalized by HPV-16.
AU Gunn G R; Zubair A; Peters C; Pan Z K; Wu T C; Paterson Y
SO JOURNAL OF IMMUNOLOGY, (2001 Dec 1) 167 (11) 6471-9.
Journal code: 2985117R. ISSN: 0022-1767.
AB Two recombinant Listeria monocytogenes (rLm) strains were produced that secrete the human papilloma virus-16 (HPV-16) E7 protein expressed in HPV-16-associated cervical cancer cells. One, Lm-E7, expresses and secretes E7 protein, whereas a second, Lm-LLO-E7, secretes E7 as a fusion protein joined to a nonhemolytic listeriolysin O (LLO). Lm-LLO-E7, but not Lm-E7, induces the regression of the E7-expressing tumor, TC-1, established in syngeneic C57BL/6 mice. Both recombinant E7-expressing rLm vaccines induce measurable anti-E7 CTL responses that stain positively for H-2D(b) E7 tetramers. Depletion of the CD8+ T cell subset before treatment abrogates the ability of Lm-LLO-E7 to impact on tumor growth. In addition, the rLm strains induce markedly different CD4+ T cell subsets. Depletion of the CD4+ T cell subset considerably reduces the ability of Lm-LLO-E7 to eliminate established TC-1 tumors. Surprisingly, the reverse is the case for Lm-E7, which becomes an effective anti-tumor immunotherapeutic in mice lacking this T cell subset. Ab-mediated depletion of TGF-beta and CD25+ cells improves the effectiveness of Lm-E7 treatment, suggesting that TGF-beta and CD25+ cells are in part responsible for this

suppressive response. CD4+ T cells from mice immunized with Lm-E7 are capable of suppressing the ability of Lm-LLO-E7 to induce the regression of TC-1 when transferred to tumor-bearing mice. These studies demonstrate the complexity of L. monocytogenes-mediated tumor immunotherapy targeting the human tumor Ag, HPV-16 E7.

L16 ANSWER 2 OF 15 MEDLINE
AN 2001492859 MEDLINE
TI Immunotherapy using heat-shock protein preparations of leukemia cells after syngeneic bone marrow transplantation in mice.
AU Sato K; Torimoto Y; Tamura Y; Shindo M; Shinzaki H; Hirai K; Kohgo Y
SO BLOOD, (2001 Sep 15) 98 (6) 1852-7.
Journal code: 7603509. ISSN: 0006-4971.
AB Heat-shock proteins (HSPs) act as molecular chaperones binding endogenous antigenic peptides and transporting them to major histocompatibility complexes. HSPs chaperone a broad repertoire of endogenous peptides including tumor antigens. For the immunotherapy of tumors, a strategy using HSPs may be more advantageous than other procedures because the identification of each tumor-specific antigen is not necessary. In this study, the efficacy of immunotherapy against minimal residual leukemia cells using HSP preparations was evaluated. HSP70 and GP96 were purified from syngeneic leukemia cell line A20 and immunized into BALB/c mice during the reconstitution period of the immune system after syngeneic bone marrow transplantation. In this procedure, all mice not immunized were dead within 60 days of A20 inoculation, whereas the survival times of HSP-immunized mice were significantly prolonged. In addition, the depletion of either CD4(+) or CD8(+) T lymphocyte significantly abrogated this efficacy, indicating that both CD4(+) and CD8(+) T lymphocytes were required for tumor cell rejection. Moreover, the vaccination of HSPs elicited a specific response of potent CD8(+) T lymphocytes cytotoxic against A20 in vitro. These observations suggest that immunization of the complex of HSPs and peptides derived from leukemia cells leads to immune responses. These immune responses are sufficient to reject minimal amounts of leukemia cells for relatively immunocompromised mice after syngeneic bone marrow transplantation.

L16 ANSWER 3 OF 15 MEDLINE
AN 2001406636 MEDLINE
TI Protective CTL response is induced in the absence of CD4+ T cells and IFN-gamma by gene gun DNA vaccination with a minigene encoding a CTL epitope of Listeria monocytogenes.
AU Yoshida A; Nagata T; Uchijima M; Koide Y
SO VACCINE, (2001 Jul 20) 19 (30) 4297-306.
Journal code: 8406899. ISSN: 0264-410X.
AB Our work was undertaken to learn the mechanism of induction of protective cytotoxic T lymphocytes (CTL) by gene gun DNA vaccination with p91m encoding an H-2Kd-restricted T cell epitope of listeriolysin O (LLO). Vaccination with p91m induced vigorous antigen-specific CD8+ CTL that produce IFN-gamma and was able to confer partial protection against listerial challenge. However, the p91m-induced protective immunity was revealed to be independent of the IFN-gamma and CD4+ T cell help. The CTL induction is also suggested to require neither adjuvant activity of the plasmid used nor IFN-gamma. The data may be feasible for the design of CTL inducing vaccines in various immunodeficiencies.

L16 ANSWER 4 OF 15 MEDLINE
AN 1999441375 MEDLINE
TI Effective DNA vaccination against listeriosis by prime/boost inoculation with the gene gun.
AU Fensterle J; Grode L; Hess J; Kaufmann S H
SO JOURNAL OF IMMUNOLOGY, (1999 Oct 15) 163 (8) 4510-8.
Journal code: 2985117R. ISSN: 0022-1767.
AB Protective immunity against Listeria monocytogenes strongly depends on CD8+ T lymphocytes, and both IFN-gamma secretion and target cell killing are considered relevant to protection. We analyzed whether we could induce a protective type 1 immune response by DNA vaccination with the gene gun using plasmids encoding for two immunodominant listerial Ags, listeriolysin and p60. To induce a Th1 response, we 1) coprecipitated a plasmid encoding for GM-CSF, 2) employed a prime/boost vaccination schedule with a 45-day interval, and 3) coinjected oligodeoxynucleotides (ODN) containing immunostimulatory CpG motifs. DNA immunization of BALB/c mice with plasmids encoding for listeriolysin (pChly) and p60 (pCiap) efficiently induced MHC class I-restricted, Ag-specific CD8+ T cells that produced IFN-gamma. Coinjection of CpG-ODN significantly increased the frequency of specific IFN-gamma-secreting T cells. Although pChly induced specific CD8+ T cells expressing CTL activity, it failed to stimulate CD4+ T cells. Only pCiap induced significant CD4+ T cell and humoral responses, which were predominantly of Th2 type. Vaccination with either plasmid induced protective immunity against listerial challenge, and coinjection of CpG ODN improved vaccine efficacy in some situations. This study demonstrates the feasibility of gene gun administration of plasmid DNA for inducing immunity against an intracellular pathogen for which protection primarily depends on type 1 CD8+ T cells.

L16 ANSWER 5 OF 15 MEDLINE
AN 1999141650 MEDLINE
TI Priming of CD8+ CTL effector cells in mice by immunization with a stress protein-influenza virus nucleoprotein fusion molecule.
AU Anthony L S; Wu H; Sweet H; Turnnir C; Boux L J; Mizzen L A
SO VACCINE, (1999 Jan 28) 17 (4) 373-83.
Journal code: 8406899. ISSN: 0264-410X.
AB Literature is accumulating which suggests the potential for stress proteins to form the basis of a novel vaccine technology. Immunization with mammalian tumor-derived stress proteins and their associated peptides promote anti-tumor immunity. Vaccination with HIV-1 p24 antigen fused to mycobacterial heat shock protein (Hsp) Hsp71 enhances p24-specific immunity, as measured by p24-specific antibody production and in vitro cell proliferation and cytokine induction. An ovalbumin-Hsp71 fusion protein primes ovalbumin-specific CTL activity and resistance to challenge with an ovalbumin-expressing tumor. We have extended these observations by using a mycobacterial Hsp65 fusion molecule to prime CTL specific for a viral antigen. Gene fusion constructs were generated from DNA encoding Mycobacterium bovis strain BCG Hsp65 and individual fragments of influenza virus nucleoprotein (NP) encompassing H-2Kd- and H-2Db-restricted CTL epitopes. The ability of these purified recombinant fusion proteins to prime NP-specific CTL was assessed in mice of appropriate H-2 haplotypes. We observed that adjuvant-free immunization with either fusion protein elicited significant CTL activity when administered at doses of 10-100 micrograms per mouse. An NP fusion protein made with glutathione-S-transferase failed to

elicit NP-specific CTL, indicating that the phenomenon requires Hsp65 sequences. A single immunization with the Hsp65-NP fusion protein elicited CTL activity which persisted for a minimum of 4 months post-immunization, at which time it could be boosted by a second immunization. To our knowledge, this is the first report of a member of the Hsp60 family priming for antigen-specific CTL activity when employed as a fusion protein partner.

L16 ANSWER 6 OF 15 MEDLINE
AN 1998208296 MEDLINE
TI A single nonamer from the Yersinia 60-kDa heat shock protein is the target of HLA-B27-restricted CTL response in Yersinia-induced reactive arthritis.
AU Ugrinovic S; Mertz A; Wu P; Braun J; Sieper J
SO JOURNAL OF IMMUNOLOGY, (1997 Dec 1) 159 (11) 5715-23.
Journal code: 2985117R. ISSN: 0022-1767.
AB The reason for the high association of HLA-B27 with diseases such as ankylosing spondylitis and reactive arthritis is not clear. In reactive arthritis, the triggering bacteria are known, thus allowing investigation of their interaction with HLA-B27. CTL lines derived from five patients with Yersinia-induced reactive arthritis were raised by repeated stimulation in vitro with either Yersinia-infected autologous macrophages (four patients) or pooled peptides (three patients) having the HLA-B27-binding motif. The peptides were derived from five Yersinia proteins and from the chlamydial 57-kDa heat shock protein (hsp). Cytotoxicity of T cell lines was then tested against these peptides. Lytic activity was obtained with T cells stimulated with viable Yersinia or pooled peptides. Targets successfully used for lysis were cells pulsed with peptides from the Yersinia 60-kDa hsp, but not cells pulsed with peptides from other Yersinia proteins or the chlamydial hsp. T cell lines raised with 60-kDa peptides also lysed targets infected with Yersinia. Most interestingly, all three CTL lines tested (one raised with Yersinia; two with pool of peptides) recognized only one single peptide (321-329) of seven tested from the Yersinia hsp60. Cytotoxicity occurred only when target cells were matched for HLA-B27. This identification of an immunogenic peptide derived from an arthritogenic bacterium and presented by HLA-B27 opens the way for future investigation of the role of T cells specific for this peptide or cross-reacting peptides, in the immunopathology of HLA-B27-associated diseases.

L16 ANSWER 7 OF 15 MEDLINE
AN 97459311 MEDLINE
TI Acquired immunity to an intracellular pathogen: immunologic recognition of L. monocytogenes-infected cells.
AU Bouwer H G; Barry R A; Hinrichs D J
SO IMMUNOLOGICAL REVIEWS, (1997 Aug) 158 137-46. Ref: 47
Journal code: 7702118. ISSN: 0105-2896.
AB Listeria monocytogenes (L. monocytogenes) is a pathogenic bacterium, and subclinical infection in mice is utilized as a prototypic model to investigate the development and expression of acquired resistance to facultative intracellular organisms. A key virulence factor of L. monocytogenes is the hemolysin listeriolysin O (LLO), and BALB/c mice immunized with hemolysin-secreting strains of L. monocytogenes develop specific acquired resistance, while mice immunized with hemolysin-negative strains or non-viable preparations of L. monocytogenes do not develop a protective immune response. Adoptive

transfer studies show that L. monocytogenes-immune CD8+ T cells mediate acquired resistance. The L. monocytogenes-immune CD8+ population is cytotoxic, and target cells infected with hemolysin-secreting strains of L. monocytogenes are lysed, while target cells infected with hemolysin-negative strains or non-viable preparations of L. monocytogenes are not lysed. MHC class Ia and Ib molecules present L. monocytogenes-derived peptides, and we have identified Qa-Ib, a T-region-encoded MHC class Ib molecule, as a restriction element for L. monocytogenes-specific CD8+ CTL. MHC class Ib-restricted CTL are stimulated following infection with L. monocytogenes and are a significant component of the total MHC class I-restricted CTL population. These findings support the observation that cytoplasmic L. monocytogenes-derived antigens are endogenously processed and presented in association with MHC class Ia and Ib molecules to CD8+ effector cells, and that both populations of effector cells contribute to the immune response to this intracellular pathogen.

L16 ANSWER 8 OF 15 MEDLINE
AN 97297926 MEDLINE
TI Recognition of chlamydial antigen by HLA-B27-restricted cytotoxic T cells in HLA-B*2705 transgenic CBA (H-2k) mice.
AU Kuon W; Lauster R; Bottcher U; Koroknay A; Ulbrecht M; Hartmann M; Grolms M; Ugrinovic S; Braun J; Weiss E H; Sieper J
SO ARTHRITIS AND RHEUMATISM, (1997 May) 40 (5) 945-54.
Journal code: 0370605. ISSN: 0004-3591.
AB OBJECTIVE: The association of reactive arthritis (ReA) with HLA-B27 and the presence of bacterial antigen in joints with ReA suggest that bacterial peptides might be presented by the HLA-B27 molecule and thus stimulate CD8 T cells. This study was performed to investigate the B27-restricted cytotoxic T lymphocyte (CTL) response to Chlamydia trachomatis, using the model of HLA-B27 transgenic mice. METHODS: CBA (H-2k) mice homozygous for HLA-B*2705 and human beta2-microglobulin expression were immunized with C trachomatis or with the chlamydial 57-kd heat-shock protein (hsp57) coupled to latex beads. Cytotoxicity of lymphocytes from in vivo-primed transgenic mice was tested against C trachomatis-infected targets. Blocking experiments were performed with monoclonal antibodies (MAb) against class I major histocompatibility complex molecules. RESULTS: A Chlamydia-specific lysis of both B27-transfected and nontransfected target cells was observed. This response could be inhibited by anti-B27 and anti-H2 MAb. CTL from mice immunized with hsp57 were not able to lyse Chlamydia-infected target cells, and Chlamydia-specific CTL could not destroy targets loaded with hsp57. CONCLUSION: These results suggest the existence of at least 2 CTL populations in this mouse model: one recognizing peptide of bacteria-infected cells restricted by HLA-B*2705 and the other recognizing peptide of bacteria-infected cells restricted by the murine H-2Kk molecule. It does not appear that hsp57 is a major target for the CD8 T cell response directed against Chlamydia. This animal model opens the way for identifying bacterial epitopes presented by HLA-B27, and might thus help to clarify the pathogenesis of B27-associated diseases.

L16 ANSWER 9 OF 15 MEDLINE
AN 96062052 MEDLINE
TI Listeriolysin generates a route for the presentation of exogenous antigens by major histocompatibility complex class I.

AU Darji A; Chakraborty T; Wehland J; Weiss S
SO EUROPEAN JOURNAL OF IMMUNOLOGY, (1995 Oct) 25 (10) 2967-71.
Journal code: 1273201. ISSN: 0014-2980.
AB We have exploited the pore forming activity of listeriolysin, the hemolysin of Listeria monocytogenes, to activate CD8+ T cells with soluble proteins in vivo and in vitro. Immunization with soluble, hemolytically active listeriolysin induces both cytotoxic CD8+ T cells and CD4+ T cells, and the CD8+ T cells can be propagated with soluble listeriolysin in vitro. Moreover, conventional antigens like ovalbumin mixed together with listeriolysin are also efficiently introduced into the MHC class I pathway in vitro and in vivo. Hence, listeriolysin effectively directs itself and passenger molecules into the intracellular compartment that leads to the cytotoxic T cell response. In this way, we circumvent the bias of CD8+ T cells to recognize intracellular antigens presented by major histocompatibility complex class I molecules. As cytotoxic CD8+ T cells are of pivotal importance in eliminating viral and microbial pathogens, the findings reported here could prove to be useful in vaccine development.

L16 ANSWER 10 OF 15 MEDLINE
AN 95053755 MEDLINE
TI Delivery of a viral antigen to the class I processing and presentation pathway by Listeria monocytogenes.
AU Ikonomidis G; Paterson Y; Kos F J; Portnoy D A
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1994 Dec 1) 180 (6) 2209-18.
Journal code: 2985109R. ISSN: 0022-1007.
AB Listeria monocytogenes is a facultative intracellular pathogen that grows in the cytoplasm of infected host cells. We examined the capacity of L. monocytogenes to introduce influenza nucleoprotein (NP) into the class I pathway of antigen presentation both in vitro and in vivo. Recombinant L. monocytogenes secreting a fusion of listeriolysin O and NP (LLO-NP) targeted infected cells for lysis by NP-specific class I-restricted cytotoxic T cells. Antigen presentation occurred in the context of three different class I haplotypes in vitro. A hemolysin-negative L. monocytogenes strain expressing LLO-NP was able to present in a class II-restricted manner. However, it failed to target infected cells for lysis by CD8+ T cells, indicating that hemolysin-dependent bacterial escape from the vacuole is necessary for class I presentation in vitro. Immunization of mice with a recombinant L. monocytogenes strain that stably expressed and secreted LLO-NP induced NP-specific CD8+ cytotoxic T lymphocytes. These studies have implications for the use of L. monocytogenes to deliver potentially any antigen to the class I pathway in vivo.

L16 ANSWER 11 OF 15 MEDLINE
AN 93105395 MEDLINE
TI Autoreactive and heat shock protein 60-recognizing CD4+ T-cells show antitumor activity against syngeneic fibrosarcoma.
AU Harada M; Matsuzaki G; Yoshikai Y; Kobayashi N; Kurosawa S; Takimoto H; Nomoto K
SO CANCER RESEARCH, (1993 Jan 1) 53 (1) 106-11.
Journal code: 2984705R. ISSN: 0008-5472.
AB A CD4+ heat shock protein (hsp) 60-recognizing autoreactive T-cell line (BASL1) and clone (BASL1.1) were examined for their antitumor activity against major histocompatibility complex class II-syngeneic Meth A fibrosarcoma (Meth A), which was

immunofluorescently stained with monoclonal antibody specific for hsp 60. In in vitro proliferative assay, BASL1.1 was suggested to recognize Meth A-derived hsp 60 presented by syngeneic antigen-presenting cells in a major histocompatibility complex class II-restricted manner. This cell line and clone showed antitumor activity in tumor-neutralizing (Winn) assay. BASL1 and BASL1.1 cells produced gamma-interferon, tumor necrosis factor, and interleukin 2 but not interleukin 4 by the stimulation with syngeneic spleen cells. In cytolytic assay, these cell lines and clones showed neither direct nor indirect (bystander) cytolysis against Meth A. In cytostatic assay, these cells inhibited the proliferation of Meth A in the presence of syngeneic macrophages, and this activity was abrogated by the addition of anti-gamma-interferon monoclonal antibody. Recombinant gamma-interferon could induce cytostatic activity only in the presence of macrophages, and tumor necrosis factor synergized this activity. Antitumor activity induced by BASL1 was abrogated by the administration of anti-CD8 monoclonal antibody in vivo, suggesting that CD8+ cytotoxic T-lymphocytes are essential and final effector cells for BASL1-mediated Meth A rejection. These findings indicate that CD4+ autoreactive and hsp 60-recognizing T-cells show two types of antitumor activity: cytostasis and induction of tumor-specific cytotoxic T-lymphocytes. Furthermore, these results imply that tumor-specific immunity could be elicited by CD4+ helper T-cells which recognize hsp.

L16 ANSWER 12 OF 15 MEDLINE
AN 90278355 MEDLINE
TI Specific killing of cytotoxic T cells and antigen-presenting cells by CD4+ cytotoxic T cell clones. A novel potentially immunoregulatory T-T cell interaction in man.
AU Ottenhoff T H; Mutis T
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1990 Jun 1) 171 (6) 2011-24. Journal code: 2985109R. ISSN: 0022-1007.
AB Mycobacterial antigens not only stimulate Th cells that produce macrophage-activating factors, but also CD4+ and CD8+ CTL that lyse human macrophages. The mycobacterial recombinant 65-kD hsp was previously found to be an important target antigen for polyclonal CD4+ CTL. Because of the major role of 65-kD hsp in the immune response to mycobacterial as well as autoantigens, we have studied CTL activity to this protein at the clonal level. HLA-DR or HLA-DQ restricted, CD4+CD8- T cell clones that recognize different peptides of the M. leprae 65-kD hsp strongly lysed EBV-BLCL pulsed with specific but not irrelevant peptide. No bystander lysis of B cells, T cells, or tumor cells was seen. Target cell lysis could not be triggered by PMA + Ca2+ ionophore alone and depended on active metabolism. Interestingly, these CD4+ CTL also strongly lysed themselves and other HLA-class II compatible CD4+ (TCR-alpha/beta or -gamma/delta) or CD8+ CTL clones in the presence of peptide, suggesting that CTL are not actively protected from CTL-mediated lysis. Cold target competition experiments suggested that EBV-BLCL targets were more efficiently recognized than CD4+ CTL targets. These results demonstrate that hsp65 peptide-specific HLA class II-restricted CD4+ T cell clones display strong peptide-dependent cytolytic activity towards both APCs, and, unexpectedly, CD4+ and CD8+ CTL clones, including themselves. Since, in contrast to murine T cells human T cells express class II, CTL-mediated T cell killing may represent a novel immunoregulatory pathway in man.

L16 ANSWER 13 OF 15 MEDLINE
AN 90184208 MEDLINE
TI Induction of antigen-specific CD4+ HLA-DR-restricted cytotoxic T lymphocytes as well as nonspecific nonrestricted killer cells by the recombinant mycobacterial 65-kDa heat-shock protein.
AU Ab B K; Kiessling R; Van Embden J D; Thole J E; Kumararatne D S; Pisa P; Wondimu A; Ottenhoff T H
SO EUROPEAN JOURNAL OF IMMUNOLOGY, (1990 Feb) 20 (2) 369-77.
Journal code: 1273201. ISSN: 0014-2980.
AB Acquired cell-mediated immunity to intracellular parasites like mycobacteria is dependent on antigen-specific T lymphocytes. We have recently found that mycobacteria not only induce helper T cells but also cytotoxic CD4+ and/or CD8+ T cells as well as nonspecific killer cells that lyse human macrophages in vitro. In addition, we have described that the recombinant heat-shock protein (hsp) 65 of Mycobacterium bovis BCG/M, tuberculosis is an important target antigen for CD4+CD8- cytotoxic T cells. We have now further investigated the cytotoxic effector cells that are induced by the hsp65 of BCG. Purified protein derivative of tuberculin (PPD)- or hsp65-specific cytotoxic T cells specifically lysed PPD, hsp65 of BCG and hsp65 of M. leprae-pulsed macrophages in an HLA-DR-restricted manner. Nonpulsed macrophages were lysed to a much lower but still significant extent. hsp65-induced effector cells expressed CD3, CD5, CD4, CD8 and CD56 markers. Depletion experiments showed that the antigen-specific HLA-DR-restricted killer cell was of the CD5+CD4+CD8-CD56- phenotype. Experiments using N-terminal truncated hsp65 fusion (cro-lacZ) proteins suggested that the N-terminal 65 amino acid residues of the 540 amino acid molecule are critical for the expression of the cytotoxic target epitope(s) in two individuals tested. In addition to inducing antigen-specific cytotoxic effector cells, the hsp65 also triggered nonspecific nonrestricted effector cells with lytic activity against nonpulsed autologous or allogeneic macrophages as well as K-562 and Daudi tumor cells. hsp65-stimulated effector cells produced both interferon and tumor necrosis factor-alpha. An important finding was that hsp65-stimulated effector cells strongly inhibited colony-forming unit formation from live BCG-infected autologous macrophages.

L16 ANSWER 14 OF 15 MEDLINE
AN 90116953 MEDLINE
TI Cell-mediated immunity to mycobacteria: a double-sided sword?.
AU Kaufmann S H; Flesch I E; Munk M E; Wand-Wurttenberger A; Schoel B; Koga T
SO RHEUMATOLOGY INTERNATIONAL, (1989) 9 (3-5) 181-6.
Journal code: 8206885. ISSN: 0172-8172.
AB Mycobacteria are intracellular pathogens capable of replicating in resting macrophages. Specific helper T lymphocytes which activate antimycobacterial capacities in infected macrophages represent an important constituent of acquired resistance. In addition, cytolytic T lymphocytes may contribute to resistance. On the other hand, lysis of infected host cells may also comprise autoaggressive consequences. Recent evidence suggest that T cells with specificity for mycobacterial heat shock proteins are involved in the antimycobacterial immune response. Heat shock proteins are evolutionarily highly conserved and cross-reactivity between microbial and mammalian molecules may occur on the B-cell and T-cell level. Thus, T cells directed against shared epitopes of

mycobacterial and autologous origin could initiate autoimmune reactions.

L16 ANSWER 15 OF 15 MEDLINE
AN 89036011 MEDLINE
TI The recombinant 65-kD heat shock protein of Mycobacterium bovis Bacillus Calmette-Guerin/M. tuberculosis is a target molecule for CD4+ cytotoxic T lymphocytes that lyse human monocytes.
AU Ottenhoff T H; Ab B K; Van Embden J D; Thole J E; Kiessling R
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1988 Nov 1) 168 (5) 1947-52. Journal code: 2985109R. ISSN: 0022-1007.
AB Since little is known about Tc cells in the human immune response to intracellular parasites, we have studied the role of Tc cells in response to M. bovis Bacillus Calmette-Guerin (BCG). Donors whose PBMC responded to BCG, purified protein derivative (PPD), and the recombinant 65-kD heat shock protein (HSP) of BCG generated BCG/PPD-specific CD4+ effector T lymphocytes that lysed PPD as well as recombinant 65-kD-pulsed monocytes. Nonpulsed or irrelevant antigen-pulsed target cells were lysed to a much lower but still significant extent. PPD-stimulated effector lymphocytes of a recombinant 65-kD nonresponder lysed PPD but not recombinant 65-kD-pulsed monocytes. Recombinant 65-kD-educated effector lymphocytes lysed both recombinant 65-kD- and PPD-pulsed monocytes. In addition, these effector cells efficiently lysed nonpulsed target cells. These results demonstrate that in recombinant 65-kD responders, the recombinant 65-kD HSP of BCG is an immunodominant target as well as a triggering molecule for BCG/PPD-specific CD4+ cytotoxic T cells that lyse autologous monocytes. The implications of these findings with respect to the role of the 65-kD HSP in autoimmunity are discussed.

(FILE 'HCAPLUS' ENTERED AT 10:00:02 ON 07 NOV 2002)
L1 524 SEA FILE=REGISTRY ABB=ON PLU=ON HEAT SHOCK PROTEIN?/CN

L2 17545 SEA FILE=HCAPLUS ABB=ON PLU=ON L1 OR HSP OR HEAT SHOCK PROTEIN OR HSP65 OR HSP70 OR HSP90
L17 404 SEA FILE=HCAPLUS ABB=ON PLU=ON (CD8 OR CD 8)(1W)(CYTOTO X? T CELL)
L18 7 SEA FILE=HCAPLUS ABB=ON PLU=ON L2 AND L17
L19 7 SEA FILE=HCAPLUS ABB=ON PLU=ON L18 AND (PROTEIN OR PEPTIDE OR POLYPROTEIN OR POLYPEPTIDE OR GLYCOPROTEIN OR CARBOHYDRATE OR ANTIGEN OR LIPID)

L20 5 L19 NOT L6

L20 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:124400 HCAPLUS
DOCUMENT NUMBER: 136:277754
TITLE: Minor histocompatibility **antigen** -specific MHC-restricted CD8 T cell responses elicited by **heat shock proteins**
AUTHOR(S): Robert, Jacques; Gantress, Jennifer; Rau, Laura; Bell, Alisa; Cohen, Nicholas
CORPORATE SOURCE: Department of Microbiology and Immunology, University of Rochester Medical Center, Rochester, NY, 14642, USA

SOURCE: Journal of Immunology (2002), 168(4), 1697-1703
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In mammals, the **heat shock proteins** (**HSP**) gp96 and **hsp70** elicit potent specific MHC class I-restricted CD8+ T cell (CTL) response to exogenous **peptides** they chaperone. The authors show in this study that in the adult frog Xenopus, a species whose common ancestors with mammals date back 300 million years, both **hsp70** and gp96 generate an adaptive specific cellular immune response against chaperoned minor histocompatibility antigenic **peptides** that effects an accelerated rejection of minor histocompatibility-locus disparate skin grafts in vivo and an MHC-specific **CD8** + **cytotoxic T cell** response in vitro. In naturally class I-deficient but immunocompetent Xenopus larvae, gp96 also generates an antitumor immune response that is independent of chaperoned **peptides** (i.e., gp96 purified from normal tissue also generates a significant antitumor response); this suggests a prominent contribution of an innate type of response in the absence of MHC class I Ags.

REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:340161 HCAPLUS
DOCUMENT NUMBER: 136:36252

TITLE: Immunohistochemical study of leukocyte infiltration and expression of **hsp70** in esophageal squamous cell carcinoma

AUTHOR(S): Takeno, Shinsuke; Noguchi, Tsuyoshi; Kikuchi, Ryuichi; Wada, Shinsuke; Sato, Tetsuro; Uchida, Yuzo
CORPORATE SOURCE: Department of Surgery II, Oita Medical University, Oita, 879-5593, Japan

SOURCE: Oncology Reports (2001), 8(3), 585-590
CODEN: OCRPEW; ISSN: 1021-335X
PUBLISHER: Oncology Reports
DOCUMENT TYPE: Journal
LANGUAGE: English

AB It is reported that macrophages and CD4+ or **CD8+** **cytotoxic T cells** have an important role in the suppression of cancer progression. The aim of this study was to clarify these immune responses in patients with esophageal cancer. We enrolled 28 patients with pT2 esophageal cancer that had been resected without preoperative adjuvant therapy. The correlations between the nos. of infiltrating CD4+, CD8+ and CD68+ cells, the expression of **heat shock** **protein** 70 (**hsp70**) and a variety of clinicopathol. factors were analyzed. The nos. of CD8+ T cells and CD68+ macrophages showed a significant pos. correlation with tumor diam. and the expression of **hsp70** and a neg. correlation with lymph node metastasis. The expression of **hsp70** exhibited a neg. correlation with lymph node metastasis. CD8+ T cells and CD68+ macrophages might have a suppressive function against esophageal cancer progression. Our results suggested that

hsp70 might play an important role in the presentation of tumor specific **antigens**.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:231963 HCAPLUS
DOCUMENT NUMBER: 133:16076
TITLE: Induction of cellular immunity by immunization with novel hybrid **peptides** complexed to **heat shock protein** 70
AUTHOR(S): Moroi, Yoichi; Mayhew, Mark; Trcka, Jiri; Hoe, Mee H.; Takechi, Yoshizumi; Hartl, F. Ulrich; Rothman, James E.; Houghton, Alan N.
CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, Sloan-Kettering Institute, New York, NY, 10021, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2000), 97(7), 3485-3490
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Heat shock proteins** 70 (**hsp70**) derived from tissues and cells can elicit cytotoxic T lymphocyte (CTL) responses against **peptides** bound to **hsp70**. However, **peptides** can markedly differ in their affinity for **hsp**, and this potentially limits the repertoire of **peptides** available to induce CTL by the **hsp** immunization. Hybrid **peptides** consisting of a high-affinity ligand for the **peptide**-binding site of **hsp70** joined to T cell epitopes by a glycine-serine-glycine linker were constructed. Immunization with hybrid **peptides** complexed to mouse **hsp70** effectively primed specific CTL responses in mice and were more potent than T cell **peptide** epitopes alone with **hsp70**. In vivo immunization with **hsp70** and hybrid **peptides** led to rejection of tumors expressing **antigen** with greater efficacy than immunization with **peptide** epitope plus **hsp70**. Induction of CTL responses occurred independently of CD4+ T cells, suggesting that immunization directly primed **antigen**-presenting cells to elicit **CD8+ cytotoxic T cell** responses without T cell help. Both **peptide/hsp70** complexes and mouse **hsp70** alone were able to induce cultures of mouse bone marrow-derived dendritic cells (DC) to release cytokines, including DC from endotoxin-resistant C57BL/10Sc mice. Thus, **hsp70**/hybrid **peptide** complexes can activate DC for cytokine release, providing a potential adjuvant effect that could bypass T cell help.
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

NSWER 4 OF 5 HCAPLUS COPYRIGHT 2002 ACS
ON NUMBER: 1998:195155 HCAPLUS

DOCUMENT NUMBER: 128:202134
TITLE: Isolation of processed, H-2Kb-binding ovalbumin-derived **peptides** associated with the stress **proteins HSP70** and GP96
AUTHOR(S): Breloer, Minka; Marti, Thomas; Fleischer, Bernhard; Von Bonin, Arne
CORPORATE SOURCE: Bernhard-Nocht Institute Tropical Medicine, Hamburg, D-20359, Germany
SOURCE: European Journal of Immunology (1998), 28(3), 1016-1021
CODEN: EJIMAF; ISSN: 0014-2980
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Stress-induced **proteins** or **heat shock proteins** (**HSP**) of 96 kDa mass (gp96) and 70 kDa mass (**HSP70**) were shown previously to elicit specific immunity to tumors from which they are isolated. This immunity is dependent on **CD8+ cytotoxic T cells** which are readily primed in vivo by immunization with **HSP**. The immunization capacity of **HSP** relies on their ability to bind antigenic **peptides**. The authors show that **HSP70** and gp96 prepns. purified from the ovalbumin (OVA)-transfected cell line E.G7 are assocd. with processed H-2Kb-binding **peptides** which contain the major H-2Kb-assocd. epitope SIINFEKL (OVA257-264). The data show for the 1st time in the well-defined OVA **antigen** system that not only endoplasmic reticulum-resident **HSP**, like gp96, are assocd. with processed antigenic **peptides** but that also the cytosolic **HSP70 protein** forms complexes with major finally processed MHC-binding epitopes.

L20 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:176606 HCAPLUS
DOCUMENT NUMBER: 112:176606
TITLE: Induction of **antigen**-specific CD4+ HLA-DR-restricted cytotoxic T lymphocytes as well as nonspecific nonrestricted killer cells by the recombinant mycobacterial 65-kDa **heat-shock protein**
AUTHOR(S): Ab, Birhane Kale; Kiessling, Rolf; Van Embden, Jan D. A.; Thole, Jelle E. R.; Kumararatne, Dinakantha S.; Pisa, Pavel; Wondimu, Assefa; Ottenhoff, Tom H. M.
CORPORATE SOURCE: Armauer Hansen Res. Inst., Addis Ababa, Ethiopia
SOURCE: European Journal of Immunology (1990), 20(2), 369-77
CODEN: EJIMAF; ISSN: 0014-2980
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Acquired cell-mediated immunity to intracellular parasites like [illegible]cobacteria is dependent on **antigen**-specific T [illegible]. It was recently found that mycobacteria not only [illegible]r T cells but also cytotoxic CD4+ and/or CD8+ T cells as [illegible]specific killer cells that lyse human macrophage in [illegible] recombinant **heat-shock** [illegible]p) 65 of Mycobacterium bovis BCG/M.

Searcher : Shears 308-4994

tuberculosis is an important target **antigen** for CD4+ **CD8- cytotoxic T cells**. The cytotoxic effector cells that are induced by the **hsp65** of BCG were further investigated. Purified **protein** deriv. of tuberculin (PPD)- or **hsp65**-specific cytotoxic T cells specifically lysed PPD, **hsp65** or BCG, and **hsp65** of M. leprae-pulsed macrophages in an HLA-DR-restricted manner. Nonpulsed macrophages were lysed to a much lower but still significant extent. Hps65-induced effector cells expressed CD3, CD5, CD4, CD8 and CD56 markers. Depletion expts. showed that the **antigen**-specific HLA-DR-restricted killer cell was of the CD5+CD4+CD8-CD56- phenotype. Expts. using N-terminal truncated **hsp65** fusion (cro-lacZ) **proteins** suggested that the N-terminal 65 amino acid residues of the 540 amino acid mol. are crit. for the expression of the cytotoxic epitope(s). The **hsp65** also triggered nonspecific nonrestricted effector cells with lytic activity against nonpulsed autologous or allogeneic macrophages as well as K-562 and Daudi tumor cells. **Hsp65** -stimulated effector cells produced both interferon and tumor necrosis factor-.alpha.. **Hsp65**-stimulated effector cells strongly inhibited colony-forming unit formation from live BCG-infected autologous macrophages.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 10:02:07 ON 07 NOV 2002)

L21 35 S L19
L22 27 S L21 NOT L7
L23 11 DUP REM L22 (16 DUPLICATES REMOVED)

L23 ANSWER 1 OF 11 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002094221 MEDLINE
DOCUMENT NUMBER: 21681677 PubMed ID: 11823499
TITLE: Minor histocompatibility **antigen**-specific MHC-restricted CD8 T cell responses elicited by **heat shock proteins**.
AUTHOR: Robert Jacques; Gantress Jennifer; Rau Laura; Bell Alisa; Cohen Nicholas
CORPORATE SOURCE: Department of Microbiology and Immunology, University of Rochester Medical Center, Rochester, NY 14642, USA.. robert@uhura.rochester.edu
CONTRACT NUMBER: CA-76312 (NCI)
R01 AI-44011 (NIAID)
SOURCE: JOURNAL OF IMMUNOLOGY, (2002 Feb 15) 168 (4) 1697-703.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020202
Last Updated on STN: 20020305
Entered Medline: 20020304

AB In mammals, the **heat shock proteins** (**HSP**) gp96 and **hsp70** elicit potent specific MHC class I-restricted CD8(+) T cell (CTL) response to exogenous **peptides** they chaperone. We show in this study that in the adult frog Xenopus, a species whose common ancestors with mammals

date back 300 million years, both **hsp70** and gp96 generate an adaptive specific cellular immune response against chaperoned minor histocompatibility antigenic **peptides** that effects an accelerated rejection of minor histocompatibility-locus disparate skin grafts in vivo and an MHC-specific **CD8**(+) **cytotoxic T cell** response in vitro. In naturally class I-deficient but immunocompetent Xenopus larvae, gp96 also generates an antitumor immune response that is independent of chaperoned **peptides** (i.e., gp96 purified from normal tissue also generates a significant antitumor response); this suggests a prominent contribution of an innate type of response in the absence of MHC class I Ags.

L23 ANSWER 2 OF 11 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001382771 MEDLINE
DOCUMENT NUMBER: 21192925 PubMed ID: 11295085
TITLE: Immunohistochemical study of leukocyte infiltration and expression of **hsp70** in esophageal squamous cell carcinoma.
AUTHOR: Takeno S; Noguchi T; Kikuchi R; Wada S; Sato T; Uchida Y
CORPORATE SOURCE: Department of Surgery II, Oita Medical University, Hasama-machi, Oita 879-5593, Japan.. surg2@oita-med.ac.jp
SOURCE: ONCOLOGY REPORTS, (2001 May-Jun) 8 (3) 585-90. Journal code: 9422756. ISSN: 1021-335X.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010709
Last Updated on STN: 20010709
Entered Medline: 20010705

AB It is reported that macrophages and CD4+ or **CD8+** **cytotoxic T cells** have an important role in the suppression of cancer progression. The aim of this study was to clarify these immune responses in patients with esophageal cancer. We enrolled 28 patients with pT2 esophageal cancer that had been resected without preoperative adjuvant therapy. The correlations between the numbers of infiltrating CD4+, CD8+ and CD68+ cells, the expression of **heat shock** **protein** 70 (**hsp70**) and a variety of clinicopathologic factors were analyzed. The numbers of CD8+ T cells and CD68+ macrophages showed a significant positive correlation with tumor diameter ($p = 0.01$, $p = 0.037$) and the expression of **hsp70** ($p = 0.01$, $p = 0.02$) and a negative correlation with lymph node metastasis ($p = 0.0079$, $p < 0.0001$). The expression of **hsp70** exhibited a negative correlation with lymph node metastasis ($p = 0.023$). CD8+ T cells and CD68+ macrophages might have a suppressive function against esophageal cancer progression. Our results suggested that **hsp70** might play an important role in the presentation of tumor specific **antigens**.

L23 ANSWER 3 OF 11 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2000202662 MEDLINE
DOCUMENT NUMBER: 20202662 PubMed ID: 10725409
TITLE: Induction of cellular immunity by immunization with

novel hybrid **peptides** complexed to **heat shock protein** 70.

AUTHOR: Moroi Y; Mayhew M; Trcka J; Hoe M H; Takechi Y; Hartl F U; Rothman J E; Houghton A N

CORPORATE SOURCE: Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.

SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2000 Mar 28) 97 (7) 3485-90.
Journal code: 7505876. ISSN: 0027-8424.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200004

ENTRY DATE: Entered STN: 20000505
Last Updated on STN: 20000505
Entered Medline: 20000424

AB **Heat shock proteins** 70 (**hsp70**) derived from tissues and cells can elicit cytotoxic T lymphocyte (CTL) responses against **peptides** bound to **hsp70**. However, **peptides** can markedly differ in their affinity for **hsp**, and this potentially limits the repertoire of **peptides** available to induce CTL by the **hsp** immunization. Hybrid **peptides** consisting of a high-affinity ligand for the **peptide**-binding site of **hsp70** joined to T cell epitopes by a glycine-serine-glycine linker were constructed. Immunization with hybrid **peptides** complexed to mouse **hsp70** effectively primed specific CTL responses in mice and were more potent than T cell **peptide** epitopes alone with **hsp70**. In vivo immunization with **hsp70** and hybrid **peptides** led to rejection of tumors expressing **antigen** with greater efficacy than immunization with **peptide** epitope plus **hsp70**. Induction of CTL responses occurred independently of CD4(+) T cells, suggesting that immunization directly primed **antigen**-presenting cells to elicit **CD8**(+) **cytotoxic T cell** responses without T cell help. Both **peptide/hsp70** complexes and mouse **hsp70** alone were able to induce cultures of mouse bone marrow-derived dendritic cells (DC) to release cytokines, including DC from endotoxin-resistant C57BL/10Sc mice. Thus, **hsp70**/hybrid **peptide** complexes can activate DC for cytokine release, providing a potential adjuvant effect that could bypass T cell help.

L23 ANSWER 4 OF 11 MEDLINE

ACCESSION NUMBER: 1998425522 MEDLINE

DOCUMENT NUMBER: 98425522 PubMed ID: 9754551

TITLE: Efficient induction of cytotoxic CD8+ T cells against exogenous **proteins**: establishment and characterization of a T cell line specific for the membrane **protein** ActA of Listeria monocytogenes.

AUTHOR: Bruder D; Darji A; Gakamsky D M; Chakraborty T; Pecht I; Wehland J; Weiss S

CORPORATE SOURCE: Department of Cell Biology and Immunology, GBF, National Research Center for Biotechnology, Braunschweig, Germany.. dbr@gbf.de

SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1998 Sep) 28 (9) 2630-9.
Journal code: 1273201. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981021
Last Updated on STN: 19981021
Entered Medline: 19981013

AB The property of listeriolysin (LLO) to introduce soluble passenger **proteins** into the cytosol of **antigen**-presenting cells allows the induction of **CD8+ cytotoxic T cells** against such **antigens**. To overcome the potential problem of presentation of the immunodominant epitope LL091-99 by H-2Kd, a variant LLO92A was established in which Tyr 92 was replaced by Ala. Immunization of BALB/c mice with purified LLO92A failed to stimulate cytotoxic T cells specific for either the epitope LLO91-99 or for any other LLO-derived **peptide**. Injection of mixtures of purified LLO92A and soluble nucleoprotein (NP) of influenza virus into mice resulted in a strong cytotoxic T cell response exclusively directed against NP. The LLO92A variant was successfully used to generate, propagate and characterize a CD8 T cell line specific for the membrane-bound virulence factor ActA of Listeria monocytogenes. Interestingly, wildtype ActA bound to the surface of live L. monocytogenes was not presented by MHC class I molecules to the CD8+ T cell line.

L23 ANSWER 5 OF 11 MEDLINE DUPLICATE 4

ACCESSION NUMBER: 1998202678 MEDLINE
DOCUMENT NUMBER: 98202678 PubMed ID: 9541597
TITLE: Isolation of processed, H-2Kb-binding ovalbumin-derived **peptides** associated with the stress **proteins HSP70** and gp96.
AUTHOR: Breloer M; Marti T; Fleischer B; von Bonin A
CORPORATE SOURCE: Bernhard-Nocht Institute for Tropical Medicine, Hamburg, Germany.
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1998 Mar) 28 (3) 1016-21.
Journal code: 1273201. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980430
Last Updated on STN: 19980430
Entered Medline: 19980423

AB Stress-induced **proteins** or **heat shock proteins** (**HSP**) of 96 kDa mass (gp96) and 70 kDa mass (**HSP70**) have been shown previously to elicit specific immunity to tumors from which they are isolated. This immunity is dependent on **CD8+ cytotoxic T cells** which are readily primed in vivo by immunization with **HSP**. The immunization capacity of **HSP** relies on their ability to bind antigenic **peptides**. Here we show

that **HSP70** and gp96 preparations purified from the ovalbumin (OVA)-transfected cell line E.G7 are associated with processed H-2Kb-binding **peptides** which contain the major H-2Kb-associated epitope SIINFEKL (OVA257-264). Our data show for the first time in the well-defined OVA **antigen** system that not only endoplasmic reticulum-resident **HSP**, like gp96, are associated with processed antigenic **peptides** but that also the cytosolic **HSP70 protein** forms complexes with major finally processed MHC-binding epitopes.

L23 ANSWER 6 OF 11 MEDLINE
ACCESSION NUMBER: 94246176 MEDLINE
DOCUMENT NUMBER: 94246176 PubMed ID: 8189053
TITLE: An H2-T MHC class Ib molecule presents Listeria monocytogenes-derived **antigen** to immune **CD8+ cytotoxic T cells**.
AUTHOR: Bouwer H G; Lindahl K F; Baldridge J R; Wagner C R; Barry R A; Hinrichs D J
CORPORATE SOURCE: Earle A. Chiles Research Institute, Providence Medical Center, Portland, OR 97213.
CONTRACT NUMBER: AI23455 (NIAID)
SOURCE: JOURNAL OF IMMUNOLOGY, (1994 Jun 1) 152 (11) 5352-60. Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199406
ENTRY DATE: Entered STN: 19940629
Last Updated on STN: 19990129
Entered Medline: 19940621

AB Mouse spleen T cells can adoptively transfer immunity to Listeria monocytogenes; this activity was markedly enhanced by stimulation with Con A in vitro before transfer. The enhanced and prolonged protection against L. monocytogenes in vivo was correlated with enhanced lysis in vitro of target cells infected with strains of L. monocytogenes that produce listeriolysin O (LLO). One of the targets of such cytotoxic cells from BALB/c (H2d) mice was a **peptide** that corresponded to amino acids 91 to 99 (p91-99) of the LLO molecule, which satisfies the binding motif of H2-Kd. Listeria-immune CD3+CD8+, but not CD3+CD8-, cells could also lyse H-2-incompatible, infected target cells. Immune cells from C57BL/6 (H2b) mice lysed allogeneic H-2d target cells infected with L. monocytogenes or a Bacillus subtilis transformant that secretes LLO, but did not lyse targets pulsed with p91-99. This H2-unrestricted cytolysis was therefore directed at a fragment of the LLO molecule other than p91-99. Listeria-infected bone marrow macrophages from congenic and recombinant strains of mice were lysed only when they shared the H2-T region or were Qa1-compatible with the immune cytotoxic cells; sharing of the H2-D, Q, or M region was insufficient. Thus, the immune response to L. monocytogenes included cytolytic CD8+ cells that recognized endogenously processed Listeria-derived Ags in the context of the class Ia H2-K molecule, as well as a class Ib H2-T molecule.

L23 ANSWER 7 OF 11 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 95158599 MEDLINE

DOCUMENT NUMBER: 95158599 PubMed ID: 7855326
TITLE: Immune manifestations of inflammatory muscle disease.
AUTHOR: Targoff I N
CORPORATE SOURCE: University of Oklahoma Health Sciences Center, Oklahoma City.
CONTRACT NUMBER: AI27181 (NIAID)
AK32214
SOURCE: RHEUMATIC DISEASES CLINICS OF NORTH AMERICA, (1994 Nov) 20 (4) 857-80. Ref: 100
Journal code: 8708093. ISSN: 0889-857X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950322
Last Updated on STN: 19950322
Entered Medline: 19950310

AB Evidence of autoimmune muscle injury and of systemic autoimmunity is seen in PM and DM. In typical PM, a cell-mediated attack on muscle fibers by **CD8+ cytotoxic T cells** predominates, directed at an unknown **antigen**. In DM, vascular injury is prominent, with loss of muscle capillaries and ischemic muscle damage, apparently mediated by local complement activation in small muscle vessels. Although humoral immunity seems more important in the pathogenesis of DM, serum autoantibodies are commonly found in both forms. About one third of patients have MSAs, whereas others have less specific antibodies such as anti-U1RNP, often associated with overlap syndromes involving myositis. MSAs are mutually exclusive and define characteristic clinical subgroups. Antibodies to five of the aminoacyl-tRNA synthetases are each associated with an "antisynthetase syndrome" marked by myositis, ILD, arthritis, and other features, but individual patients have only a single antisynthetase. Rare autoantibodies to certain translation factors may be associated with a similar syndrome. Anti-SRP is commonly associated with severe, acute, resistant myositis, whereas anti-Mi-2, the only MSA directed at a nuclear **protein**, is specifically associated with DM. Patients with anti-PM-Scl commonly have an overlap syndrome of PM/DM and SSc. Recent studies have recognized other antibodies in PM and DM, including antibody to endothelial cells, **heat shock proteins**, and, in a high proportion of patients, a 56-kd component of a ribonucleoprotein particle. The MSAs and their **antigens** are being characterized in detail. To date, data suggest similarity of predominant epitopes between different patients and a tendency toward conformational epitopes. It is not known if the recognized autoantibodies participate in tissue injury or pathogenetic processes, but production of the MSAs appears to be linked to etiologic factors and can be a clue to understanding the disease. Although these autoimmune responses are becoming better defined, the inciting events leading to generation of these responses and development of PM and DM remain unknown.

L23 ANSWER 8 OF 11 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 93:547607 SCISEARCH

THE GENUINE ARTICLE: LV950
TITLE: INTRATHYROIDAL LYMPHOCYTE SUBSETS, INCLUDING UNUSUAL CD4+ CD8+ CELLS AND CD3(LO)TCR-ALPHA-BETA(LO)/-CD4-CD8- CELLS, IN AUTOIMMUNE THYROID-DISEASE
AUTHOR: IWATANI Y (Reprint); HIDAKA Y; MATSUZUKA F; KUMA K; AMINO N
CORPORATE SOURCE: OSAKA UNIV, SCH MED, DEPT LAB MED, SUITA, OSAKA 565, JAPAN (Reprint); KUMA HOSP, KOBE, JAPAN
COUNTRY OF AUTHOR: JAPAN
SOURCE: CLINICAL AND EXPERIMENTAL IMMUNOLOGY, (SEP 1993) Vol. 93, No. 3, pp. 430-436.
ISSN: 0009-9104.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 54

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Intrathyroidal lymphocyte subsets were analysed in 13 euthyroid patients with autoimmune thyroid disease by two-colour flow cytometry and compared with subsets in peripheral blood. In both Graves' and Hashimoto's diseases, proportions of intrathyroidal CD5- B cells were higher than in peripheral blood. The numbers of such cells were correlated with serum levels of anti-thyroid microsomal antibodies. Proportions of T cells bearing alphabeta chains of T cell receptors (TCRalphabeta+T; Talphabeta) and CD16+CD57+ natural killer (NK) cells were lower in the thyroid, but proportions of CD3(hi)TCRalphabeta-TCRgammadelta+ (Tgammadelta) cells were not different. Proportions of CD4+Leu-8- helper T cells and CD4+CD57+ germinal centre T cells were higher and proportions of CD4+Leu-8+ suppressor-inducer T cells and CD8+CD57+ or CD8+CD11b+ suppressor T cells were lower than in the blood in both diseases. Proportions of CD5+ B cells were high in Graves' disease, and proportions of **CD8**+CD11b - **cytotoxic T cells** were high in Hashimoto's disease. Unexpectedly, CD4+CD8+ cells and CD3(lo)TCRalphabeta(lo)/-CD4-CD8- cells were present in thyroid tissues of both diseases. These findings suggest that: (i) an imbalance in the numbers of regulatory T cells and of NK cells that had appeared in the thyroid resulted in the proliferation of CD5- B cells, which were related to thyroid autoantibody production; (ii) CD5+ B cells and cytotoxic T cells are important for the different pathological features in Graves' and Hashimoto's diseases, respectively; and (iii) intrathyroidal CD4+CD8+ cells and CD3(lo)TCRalphabeta(lo)/-CD4-CD8- cells may be related to the pathogenesis of autoimmune thyroid disease.

L23 ANSWER 9 OF 11 JICST-EPlus COPYRIGHT 2002 JST
ACCESSION NUMBER: 930096351 JICST-EPlus
TITLE: Recent Topics on Basic Tumor Immunology.
AUTHOR: SATO NORIYUKI; KIKUCHI KOKICHI
CORPORATE SOURCE: Sapporo Medical College
SOURCE: Gan no Rinsho (Japanese Journal of Cancer Clinics), (1992) vol. 38, no. 12, pp. 1289-1293. Journal Code: Z0928A (Fig. 2, Ref. 21)
ISSN: 0021-4949
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Commentary
LANGUAGE: Japanese
STATUS: New

AB There is an increasing body of recent evidences showing that T cell **antigen** receptors of cytotoxic T cells are virtually involved in the tumor rejection by the hosts. Because of these facts and technological improvement of the modern immunobiology, the search for the molecular nature of tumor **antigens** become at our hand. Certain hreat shock **proteins** could play an important role in the interaction with .GAMMA..DELTA. T cells. They may be presenting molecules complexed with cellular **peptides** . More critical in the tumor immunology is the MHC class I-bound antigenic **peptides** recognized by **CD(8) cytotoxic T cells**. The amino acid sequence of these **peptides** could be determined, and the relationship of their parental molecule with the oncogenesis might be clarified. (author abst.)

L23 ANSWER 10 OF 11 MEDLINE DUPLICATE 6

ACCESSION NUMBER:	91155990 MEDLINE
DOCUMENT NUMBER:	91155990 PubMed ID: 1705662
TITLE:	Polymyositis mediated by T lymphocytes that express the gamma/delta receptor.
COMMENT:	Comment in: N Engl J Med. 1991 Aug 22;325(8):587-8
AUTHOR:	Hohlfeld R; Engel A G; Ii K; Harper M C
CORPORATE SOURCE:	Neuromuscular Research Laboratory, Mayo Clinic, Rochester, MN 55905.
CONTRACT NUMBER:	NS-6277 (NINDS)
SOURCE:	NEW ENGLAND JOURNAL OF MEDICINE, (1991 Mar 28) 324 (13) 877-81. Journal code: 0255562. ISSN: 0028-4793.
PUB. COUNTRY:	United States
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:	199104
ENTRY DATE:	Entered STN: 19910428 Last Updated on STN: 19960129 Entered Medline: 19910409

AB BACKGROUND. The invasion and destruction of nonnecrotic muscle fibers by **CD8+ cytotoxic T cells** is considered a hallmark of polymyositis. In the cases of polymyositis reported so far, the autoinvasive CD8+ T cells expressed the common form of T-cell receptor for the recognition of **antigen**, the so-called alpha/beta T-cell receptor. We describe a 69-year-old man with polymyositis mediated by CD4-, CD8- T cells expressing the recently discovered, uncommon gamma/delta T-cell receptor. METHODS. We used immunofluorescence or immunoperoxidase techniques to study frozen sections of muscle from our patient, who had mild weakness of cervical and proximal limb muscles, and from control patients with polymyositis, inclusion-body myositis, dermatomyositis, or granulomatous myopathy with monoclonal antibodies against T-cell-related **antigens** (CD2, CD3, CD4, CD8, and gamma/delta T-cell receptor), B cells (CD22), major histocompatibility complex (MHC) and MHC-related **antigens** (MHC Class I, CD1a, CD1b, and CD1c), and the 65-kd **heat-shock protein**. The membrane contacts between the autoinvasive cells and the sarcolemma were investigated by electron microscopy. RESULTS. In the patient described here, but not in 28 others with inflammatory myopathies, myriad gamma/delta T cells surrounded and invaded nonnecrotic muscle fibers. All muscle fibers

were highly reactive for MHC Class I **antigen** and the 65-kd **heat-shock protein**. Treatment with prednisone improved the clinical and histologic findings. CONCLUSIONS. Polymyositis can be mediated by gamma/delta T cells. This new form of polymyositis appears to be highly responsive to steroids.

L23 ANSWER 11 OF 11 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 90184208 MEDLINE
DOCUMENT NUMBER: 90184208 PubMed ID: 1690136
TITLE: Induction of **antigen**-specific CD4+ HLA-DR-restricted cytotoxic T lymphocytes as well as nonspecific nonrestricted killer cells by the recombinant mycobacterial 65-kDa **heat-shock protein**.
AUTHOR: Ab B K; Kiessling R; Van Embden J D; Thole J E; Kumararatne D S; Pisa P; Wondimu A; Ottenhoff T H
CORPORATE SOURCE: Armauer Hansen Research Institute, Addis Ababa, Ethiopia.
CONTRACT NUMBER: AI 20198-3 (NIAID)
R01 CA 44882-1 (NCI)
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1990 Feb) 20 (2) 369-77.
Journal code: 1273201. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199004
ENTRY DATE: Entered STN: 19900601
Last Updated on STN: 19960129
Entered Medline: 19900423

AB Acquired cell-mediated immunity to intracellular parasites like mycobacteria is dependent on **antigen**-specific T lymphocytes. We have recently found that mycobacteria not only induce helper T cells but also cytotoxic CD4+ and/or CD8+ T cells as well as nonspecific killer cells that lyse human macrophages in vitro. In addition, we have described that the recombinant **heat-shock protein** (**hsp**) 65 of Mycobacterium bovis BCG/M, tuberculosis is an important target **antigen** for CD4+**CD8- cytotoxic T cells**. We have now further investigated the cytotoxic effector cells that are induced by the **hsp65** of BCG. Purified **protein** derivative of tuberculin (PPD)- or **hsp65**-specific cytotoxic T cells specifically lysed PPD, **hsp65** of BCG and **hsp65** of M. leprae-pulsed macrophages in an HLA-DR-restricted manner. Nonpulsed macrophages were lysed to a much lower but still significant extent. **hsp65**-induced effector cells expressed CD3, CD5, CD4, CD8 and CD56 markers. Depletion experiments showed that the **antigen**-specific HLA-DR-restricted killer cell was of the CD5+CD4+CD8-CD56- phenotype. Experiments using N-terminal truncated **hsp65** fusion (cro-lacZ) **proteins** suggested that the N-terminal 65 amino acid residues of the 540 amino acid molecule are critical for the expression of the cytotoxic target epitope(s) in two individuals tested. In addition to inducing **antigen**-specific cytotoxic effector cells, the **hsp65** also triggered nonspecific nonrestricted effector cells with lytic

activity against nonpulsed autologous or allogeneic macrophages as well as K-562 and Daudi tumor cells. **hsp65**-stimulated effector cells produced both interferon and tumor necrosis factor-alpha. An important finding was that **hsp65** -stimulated effector cells strongly inhibited colony-forming unit formation from live BCG-infected autologous macrophages.

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primary and metastatic neoplastic diseases and infectious diseases. The methods of the invention comprise administering a composition comprising an effective amount of a complex, in which the complex consists essentially of a **heat shock protein** (**hsp**) noncovalently bound to an antigenic molecule. "Antigenic molecule" as used herein refers to the **peptides** with which the **hsps** are endogenously associated in vivo as well as exogenous **antigens** /immunogens (i.e., with which the **hsps** are not complexed in vivo) or antigenic/immunogenic fragments and derivatives thereof. In a preferred embodiment, the complex is autologous to the individual. The effective amounts of the complex are in the range of 10-600 micrograms for complexes comprising **hsp70**, 50-1000 micrograms for **hsp90**, and 10-600 micrograms for gp96. The invention also provides a method for measuring tumor rejection in vivo in an individual, preferably a human, comprising measuring the generation by the individual of MHC Class I-restricted **CD8** + **cytotoxic T lymphocytes** specific to the tumor. Methods of purifying **hsp70-peptide** complexes are also provided.

L8 ANSWER 19 OF 45 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:236970 BIOSIS
DOCUMENT NUMBER: PREV200100236970
TITLE: Compositions and methods using complexes of **heat shock protein** 70 and antigenic molecules for the treatment and prevention of neoplastic diseases.
AUTHOR(S): Srivastava, Pramod K.
ASSIGNEE: Fordham University
PATENT INFORMATION: US 6136315 October 24, 2000
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Oct. 24, 2000) Vol. 1239, No. 4, pp. No Pagination. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
AB The present invention relates to methods and compositions for eliciting an immune response and the prevention and treatment of primary and metastatic neoplastic diseases and infectious diseases. The methods of the invention comprise administering a composition comprising an effective amount of a complex, in which the complex consists essentially of a **heat shock protein** (**hsp**) noncovalently bound to an antigenic molecule. "Antigenic molecule" as used herein refers to the **peptides** with which the **hsps** are endogenously associated in vivo as well as exogenous **antigens** /immunogens (i.e., with which the **hsps** are not complexed in vivo) or antigenic/immunogenic fragments and derivatives thereof. In a preferred embodiment, the complex is autologous to the individual. The effective amounts of the complex are in the range of 10-600 micrograms for complexes comprising **hsp70**, 50-1000 micrograms for **hsp90**, and 10-600 micrograms for gp96. The invention also provides a method for measuring tumor rejection in vivo in an individual, preferably a human, comprising measuring the generation by the individual of MHC Class I-restricted **CD8** + **cytotoxic T lymphocytes** specific to the tumor. Methods of purifying **hsp70-peptide**

complexes are also provided.

L8 ANSWER 20 OF 45 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2000:904195 SCISEARCH
THE GENUINE ARTICLE: 376PZ
TITLE: Identification of major epitopes of Mycobacterium tuberculosis AG85B that are recognized by HLA-A]0201-restricted CD8(+) T cells in HLA-transgenic mice and humans
AUTHOR: Geluk A (Reprint); vanMeijgaarden K E; Franken K L M C; Drijfhout J W; DSouza S; Necker A; Huygen K; Ottenhoff T H M
CORPORATE SOURCE: LEIDEN UNIV, MED CTR, DEPT IMMUNOHEMATOL & BLOOD TRANSFUS, POB 9600, NL-2300 RC LEIDEN, NETHERLANDS (Reprint); INST PASTEUR, DEPT MYCOBAACTERIAL IMMUNOL, BRUSSELS, BELGIUM; IMMUNOTECH SA, MARSEILLE, FRANCE
COUNTRY OF AUTHOR: NETHERLANDS; BELGIUM; FRANCE
SOURCE: JOURNAL OF IMMUNOLOGY, (1 DEC 2000) Vol. 165, No. 11, pp. 6463-6471.
Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0022-1767.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 44

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB CD8(+) T cells are thought to play an important role in protective immunity to tuberculosis. Although several nonprotein ligands have been identified for CD1-restricted **CD8**(+) **CTLs**, epitopes for classical MHC class I-restricted CD8(+) T cells, which most likely represent a majority among CD8(+) T cells, have remained ill defined. HLA-A*0201 is one of the most prevalent class I alleles, with a frequency of over 30% in most populations. HLA-A2/K-b transgenic mice were shown to provide a powerful model for studying induction of HLA-A*0201-restricted immune responses in vivo. The Ag85 complex, a major component of secreted Mycobacterium tuberculosis **proteins**, induces strong CD4(+) T cell responses in M, tuberculosis-infected individuals, and protection against tuberculosis in Ag85-DNA-immunized animals. In this study, we demonstrate the presence of HLA class I-restricted, CD8(+) T cells against Ag85B of M. tuberculosis in HLA-A2/K-b transgenic mice and HLA-A*0201(+) humans. Moreover, two immunodominant Ag85 **peptide** epitopes for HLA-A*0201-restricted, M. tuberculosis-reactive **CD8**(+) **CTLs** were identified, These CD8(+) T cells produced IFN-gamma and TNF-alpha and recognized Ag-pulsed or bacillus Calmette-Guerin-infected, HLA-A*0201-positive, but not HLA-A*0201-negative or uninfected human macrophages. This CTL-mediated killing was blocked by anti-CD8 or anti-HLA class I mAb, Using fluorescent **peptide**/HLA-A*0201 tetramers, Ag85-specific CD8(+) T cells could be visualized in bacillus calmette-Guerin-responsive, HLA-A*0201(+) individuals. Collectively, our results demonstrate the presence of HLA class I-restricted **CD8**(+) **CTL** against a major Ag of M, tuberculosis and identify Ag85B epitopes that are strongly recognized by HLA-A*0201-restricted CD8(+) T cells in humans and mice. These epitopes thus represent potential subunit components for

the design of vaccines against tuberculosis.

L8 ANSWER 21 OF 45 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2000148983 MEDLINE
DOCUMENT NUMBER: 20148983 PubMed ID: 10684306
TITLE: Recombinant adeno-associated virus expressing human papillomavirus type 16 E7 **peptide** DNA fused with **heat shock protein** DNA as a potential vaccine for cervical cancer.
AUTHOR: Liu D W; Tsao Y P; Kung J T; Ding Y A; Sytwu H K; Xiao X; Chen S L
CORPORATE SOURCE: Department of Microbiology and Immunology, Taipei, Taiwan, Republic of China.
SOURCE: JOURNAL OF VIROLOGY, (2000 Mar) 74 (6) 2888-94. Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000413
Last Updated on STN: 20000413
Entered Medline: 20000403

AB In this study, we explore a potential vaccine for human papillomavirus (HPV)-induced tumors, using **heat shock protein** as an adjuvant, a **peptide** vaccine for safety, and adeno-associated virus (AAV) as a gene delivery vector. The tumor vaccine was devised by constructing a chimeric gene which contained HPV type 16 E7 cytotoxic T-lymphocyte (CTL) epitope DNA (M. C. Feltkamp, H. L. Smits, M. P. Vierboom, R. P. Minnaar, B. M. de Jongh, J. W. Drijfhout, J. ter Schegget, C. J. Melief, and W. M. Kast, Eur. J. Immunol. 23:2242-2249, 1993) fused with the **heat shock protein** gene as a tumor vaccine delivered via AAV. Our results demonstrate that this vaccine can eliminate tumor cells in syngeneic animals and induce CD4- and **CD8**-dependent **CTL** activity in vitro. Moreover, studies with knockout mice with distinct T-cell deficiencies confirm that CTL-induced tumor protection is CD4 and CD8 dependent. Taken together, the evidence indicates that this chimeric gene delivered by AAV has potential as a cervical cancer vaccine.

L8 ANSWER 22 OF 45 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 2000105365 MEDLINE
DOCUMENT NUMBER: 20105365 PubMed ID: 10637285
TITLE: In vivo cytotoxic T lymphocyte elicitation by mycobacterial **heat shock protein** 70 fusion **proteins** maps to a discrete domain and is CD4(+) T cell independent.
AUTHOR: Huang Q; Richmond J F; Suzue K; Eisen H N; Young R A
CORPORATE SOURCE: Whitehead Institute for Biomedical Research, Cambridge, Massachusetts 02142, USA.
CONTRACT NUMBER: AI44476 (NIAID)
AI44477 (NIAID)
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (2000 Jan 17) 191 (2) 403-8. Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000309
Last Updated on STN: 20000309
Entered Medline: 20000222

AB To gain insights into the mechanisms by which soluble **heat shock protein (hsp)** fusions can elicit **CD8(+) cytotoxic T lymphocytes** (CTLs) against the fusion partner, mycobacterial (Mycobacterium tuberculosis) **hsp70** was dissected to ascertain whether a particular **hsp** domain is necessary, and knockout mice were used to determine whether the fusion **protein's** immunogenicity is dependent on CD4(+) T lymphocytes. We found that the ability to elicit **CD8**(+) **CTLs** depends on a discrete 200-amino acid **protein** domain, indicating that the fusion **protein's** immunogenicity for CD8(+) T cells does not require coupled chaperone function or **peptide** binding. Further, we found that ovalbumin (OVA).**hsp70** fusion **protein** elicited anti-OVA **CD8**(+) **CTLs** about equally well in CD4 knockout and wild-type C57BL/6 mice, and also when the **hsp70** was of murine (self) origin. The ability of **hsp70** fusion **proteins** to elicit CD4-independent CTL responses suggests that **hsp70** fusion **proteins** may be useful for immunological prophylaxis and therapy against disease in CD4(+) T cell-deficient individuals.

L8 ANSWER 23 OF 45 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 2000216389 MEDLINE
DOCUMENT NUMBER: 20216389 PubMed ID: 10755613
TITLE: A proposed mechanism for the induction of cytotoxic T lymphocyte production by heat shock fusion **proteins**.
AUTHOR: Cho B K; Palliser D; Guillen E; Wisniewski J; Young R A; Chen J; Eisen H N
CORPORATE SOURCE: Center for Cancer Research and Department of Biology, Massachusetts Institute of Technology, Cambridge 02139, USA.
CONTRACT NUMBER: 5T32-AI-07463 (NIAID)
CA-14051 (NCI)
CA-60686 (NCI)
+
SOURCE: IMMUNITY, (2000 Mar) 12 (3) 263-72.
Journal code: 9432918. ISSN: 1074-7613.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000505
Last Updated on STN: 20000505
Entered Medline: 20000426

AB A 65 kDa mycobacterial **heat shock protein (hsp65)**, fused to a **polypeptide** that contains an octapeptide (SIYRYYGL) agonist for a particular T cell receptor (2C TCR), stimulated C57BL/6 mice as well as

CD4-deficient mice to produce CD8+ cytolytic T lymphocytes (CTL) to the fusion partner's octapeptide. This and other **hsp65** fusion **proteins** but not native **hsp65** itself stimulated dendritic cells in vitro and in vivo to upregulate the levels of MHC (class I and II) and costimulatory (B7.2) molecules. The results suggest a mechanism for the general finding that **hsp** fusion **proteins**, having fusion partners of widely differing lengths and sequences, elicit **CD8** **CTL** to **peptides** from the fusion partners without requiring exogenous adjuvants or the participation of CD4+ T cells.

L8 ANSWER 24 OF 45 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 2000124181 MEDLINE
DOCUMENT NUMBER: 20124181 PubMed ID: 10655113
TITLE: Molecular mimicry mediated by MHC class Ib molecules after infection with gram-negative pathogens.
AUTHOR: Lo W F; Woods A S; DeCloux A; Cotter R J; Metcalf E S; Soloski M J
CORPORATE SOURCE: Division of Rheumatology, Department of Medicine and The Graduate Program in Immunology, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21218, USA.
CONTRACT NUMBER: RO1AI20922 (NIAID)
RO1AI32951 (NIAID)
RO1AI42287 (NIAID)
+
SOURCE: NATURE MEDICINE, (2000 Feb) 6 (2) 215-8.
Journal code: 9502015. ISSN: 1078-8956.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20000229
Entered Medline: 20000217

AB The development of many autoimmune diseases has been etiologically linked to exposure to infectious agents. For example, a subset of patients with a history of Salmonella infection develop reactive arthritis. The persistence of bacterial **antigen** in arthritic tissue and the isolation of Salmonella or Yersinia reactive CD8+ T cells from the joints of patients with reactive arthritis support the etiological link between Gram-negative bacterial infection and autoimmune disease. Models proposed to account for the link between infection and autoimmunity include inflammation-induced presentation of cryptic self-epitopes, **antigen** persistence and molecular mimicry. Several studies support molecular mimicry as a mechanism for the involvement of class II epitopes in infectious disease-induced self-reactivity. Here, we have identified an immunodominant epitope derived from the S. typhimurium GroEL molecule. This epitope is presented by the mouse H2-T23-encoded class Ib molecule Qa-1 and was recognized by **CD8+ cytotoxic T lymphocytes** induced after natural infection. S. typhimurium-stimulated cytotoxic T lymphocytes recognizing the GroEL epitope cross-reacted with a **peptide** derived from mouse **heat shock** **protein** 60 and recognized stressed macrophages. Our results indicate involvement of MHC class Ib molecules in infection-induced

autoimmune recognition and indicate a mechanism for the etiological link between Gram-negative bacterial infection and autoimmunity.

L8 ANSWER 25 OF 45 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 2000021808 MEDLINE
DOCUMENT NUMBER: 20021808 PubMed ID: 10553037
TITLE: Cutting edge: tumor secreted heat shock-fusion **protein** elicits CD8 cells for rejection.
AUTHOR: Yamazaki K; Nguyen T; Podack E R
CORPORATE SOURCE: Department of Microbiology and Immunology, University of Miami School of Medicine, FL 33101, USA.
CONTRACT NUMBER: CA39201 (NCI)
CA590351 (NCI)
CA80228 (NCI)
SOURCE: JOURNAL OF IMMUNOLOGY, (1999 Nov 15) 163 (10) 5178-82.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991202
AB The endoplasmic reticulum resident **heat shock protein** gp96 chaperons **peptides**, including those derived from tumor Ags, on their way to presentation by MHC class I. Replacement of the endoplasmic reticulum retention signal of gp96 with the Fc portion of murine IgG1 generated a secretory form of gp96, gp96-Ig. Tumor cells secreting gp96-Ig exhibited decreased tumorigenicity and increased immunogenicity in vivo and were rejected after initial growth. Rejection required CD8 T cells during the priming and effector phase. CD4 T cells were not required for rejection in either phase. Carrageenan, a compound known to inactivate macrophages in vivo, did not diminish CD8-mediated tumor rejection. Therefore, immunization with tumors secreting gp96-Ig generates efficient tumor-rejecting **CD8 CTL** without requirement for CD4 or macrophage help. In contrast, immunization with purified, tumor-derived gp96 or with irradiated tumor cells requires both.

L8 ANSWER 26 OF 45 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 1999141650 MEDLINE
DOCUMENT NUMBER: 99141650 PubMed ID: 9987177
TITLE: Priming of **CD8+ CTL** effector cells in mice by immunization with a stress **protein**-influenza virus nucleoprotein fusion molecule.
Anthony L S; Wu H; Sweet H; Turnnir C; Boux L J; Mizzen L A
StressGen Biotechnologies Corporation, Victoria, BC, Canada.. lanthony@stressgen.com
CCINE, (1999 Jan 28) 17 (4) 373-83.
nal code: 8406899. ISSN: 0264-410X.
AND: United Kingdom
urnal; Article; (JOURNAL ARTICLE)

Searcher : Shears 308-4994

LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990517
Last Updated on STN: 19990517
Entered Medline: 19990505

AB Literature is accumulating which suggests the potential for stress **proteins** to form the basis of a novel vaccine technology. Immunization with mammalian tumor-derived stress **proteins** and their associated **peptides** promote anti-tumor immunity. Vaccination with HIV-1 p24 **antigen** fused to mycobacterial **heat shock protein** (**Hsp**) Hsp71 enhances p24-specific immunity, as measured by p24-specific antibody production and in vitro cell proliferation and cytokine induction. An ovalbumin-Hsp71 fusion **protein** primes ovalbumin-specific CTL activity and resistance to challenge with an ovalbumin-expressing tumor. We have extended these observations by using a mycobacterial **Hsp65** fusion molecule to prime CTL specific for a viral **antigen**. Gene fusion constructs were generated from DNA encoding Mycobacterium bovis strain BCG **Hsp65** and individual fragments of influenza virus nucleoprotein (NP) encompassing H-2Kd- and H-2Db-restricted CTL epitopes. The ability of these purified recombinant fusion **proteins** to prime NP-specific CTL was assessed in mice of appropriate H-2 haplotypes. We observed that adjuvant-free immunization with either fusion **protein** elicited significant CTL activity when administered at doses of 10-100 micrograms per mouse. An NP fusion **protein** made with glutathione-S-transferase failed to elicit NP-specific CTL, indicating that the phenomenon requires **Hsp65** sequences. A single immunization with the **Hsp65**-NP fusion **protein** elicited CTL activity which persisted for a minimum of 4 months post-immunization, at which time it could be boosted by a second immunization. To our knowledge, this is the first report of a member of the Hsp60 family priming for **antigen**-specific CTL activity when employed as a fusion **protein** partner.

L8 ANSWER 27 OF 45 MEDLINE
ACCESSION NUMBER: 1999081750 MEDLINE
DOCUMENT NUMBER: 99081750 PubMed ID: 9864223
TITLE: Existing antilisterial immunity does not inhibit the development of a Listeria monocytogenes-specific primary cytotoxic T-lymphocyte response.
AUTHOR: Bouwer H G; Shen H; Fan X; Miller J F; Barry R A; Hinrichs D J
CORPORATE SOURCE: Immunology Research, Veterans Affairs Medical Center, Earle A. Chiles Research Institute, Portland, Oregon, USA.. bouwera@ohsu.edu
CONTRACT NUMBER: AI38955 (NIAID)
RO1 AI23455 (NIAID)
RO1 AI40698 (NIAID)
SOURCE: INFECTION AND IMMUNITY, (1999 Jan) 67 (1) 253-8.
Journal code: 0246127. ISSN: 0019-9567.
Y: United States
E: Journal; Article; (JOURNAL ARTICLE)
English
Priority Journals

Searcher : Shears 308-4994

ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990209
Last Updated on STN: 19990209
Entered Medline: 19990128

AB Infection of BALB/c mice with Listeria monocytogenes stimulates an antilisterial immune response evident by the appearance of H2-Kd-restricted **CD8(+) cytotoxic T lymphocytes** (CTLs) specific for the nanomer **peptides** amino acids (aa) 91 to 99 of listeriolysin O (LLO 91-99) and aa 217 to 225 of the p60 molecule (p60 217-225). We have introduced point mutations at anchor residues within LLO 91-99 (92F) or p60 217-225 (218F), and BALB/c mice infected with L. monocytogenes strains containing these point mutations do not develop CTLs specific for LLO 91-99 or p60 217-225, respectively. We have used these strains to test whether primary CTL responses against L. monocytogenes-derived determinants can be stimulated within an environment of existing antilisterial immunity. We found that the development of a primary L. monocytogenes-specific CTL response is not altered by existing immunity to L. monocytogenes. For example, primary immunization with the p60 218F strain of L. monocytogenes followed by a secondary immunization with wild-type L. monocytogenes results in stimulation of p60 217-225-specific CTLs at primary response levels and LLO 91-99-specific effectors at levels consistent with a memory CTL response. Similarly, primary immunization with the 92F strain of L. monocytogenes followed by a secondary immunization with wild-type L. monocytogenes results in stimulation of LLO 91-99-specific CTLs at primary response levels and p60 217-225-specific effectors at levels consistent with a memory CTL response. These results provide additional support for the use of L. monocytogenes as a recombinant vaccine vector and show that antivector immunity does not inhibit the development of a primary CTL response when the epitope is delivered by L. monocytogenes as the vaccine strain.

L8 ANSWER 28 OF 45 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:99215 BIOSIS
DOCUMENT NUMBER: PREV199900099215
TITLE: Human dendritic cells stimulate T cell responses to melanoma-derived **heat shock protein** GP96.
AUTHOR(S): Bernhard, H. (1); Fleischer, K.; Batten, W. Y.; Heike, M.; Peschel, C.
CORPORATE SOURCE: (1) III Med. Klin., Klin. Rechts Isar, Technische Univ. Muenchen, Muenchen Germany
SOURCE: Blood, (Nov. 15, 1998) Vol. 92, No. 10 SUPPL. 1 PART 1-2, pp. 542A.
Meeting Info.: 40th Annual Meeting of the American Society of Hematology Miami Beach, Florida, USA December 4-8, 1998 The American Society of Heamatology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

L8 ANSWER 29 OF 45 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 1999038070 MEDLINE
DOCUMENT NUMBER: 99038070 PubMed ID: 9822276
TITLE: Interferon-gamma (IFN-gamma) and tumour necrosis

factor-alpha (TNF-alpha) are necessary in the early stages of induction of CD4 and CD8 cytotoxic T cells by Mycobacterium leprae **heat shock protein (hsp)** 65 kD.

AUTHOR: Sasiain M C; de la Barrera S; Fink S; Finiasz M; Aleman M; Farina M H; Pizzariello G; Valdez R

CORPORATE SOURCE: Departamento de Inmunologia, IIHema., Academia Nacional de Medicina, Hospital F. J. Muniz, Buenos Aires, Argentina.

SOURCE: CLINICAL AND EXPERIMENTAL IMMUNOLOGY, (1998 Nov) 114 (2) 196-203.
Journal code: 0057202. ISSN: 0009-9104.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199812

ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981214

AB Cytotoxic T cells (CTL) may play an important role in host defence against mycobacterial infections. CD4 CTL are preferentially induced by mycobacteria, but both CD4 and **CD8 CTL** may be necessary components of a protective immune response. The 65-kD mycobacterium **heat shock protein** (**hsp65**) is a poor inducer of CTL in multibacillary leprosy (MB) patients. In this study we evaluate the possible role of cytokines in modulating the cytotoxic activity of CTL from leprosy patients and normal individuals (N) against autologous macrophages presenting Mycobacterium leprae **hsp65**. Our results show that **hsp65**-specific CTL were generated from both CD4 and CD8 lymphocytes. In N, individual cytokines as well as the combination of them were able to modify the **hsp65**-induced cytotoxic activity. The effect of cytokines on leprosy patients' lymphocytes was different in MB and paucibacillary (PB) patients. Thus, IL-6, IL-2, IFN-gamma or TNF-alpha did not modify the generation of **hsp65**-CTL from either MB (with or without an erythema nodosum episode (ENL)) or PB. In all the patients the simultaneous addition of two cytokines was required in order to increase CTL generation. In MB, IL-6 plus IFN-gamma or IL-2 increased both CD4 and **CD8 CTL**, while TNF-alpha plus IFN-gamma up-regulated only CD4 CTL. In PB, **CD8 CTL** were prominent with IL-6 plus IFN-gamma, while the increase was significant in CD4 CTL with IL-6 plus IL-2. Down-regulation of CTL was observed by addition of IL-4, IL-10, anti-IFN-gamma or anti-TNF-alpha in N controls. Our data demonstrate that IFN-gamma and TNF-alpha must be present for at least the first 60 h of the induction stage in order to generate full **hsp65** CTL. Hence, IFN-gamma and TNF-alpha would be key factors in the generation of **hsp65** CTL.

L8 ANSWER 30 OF 45 MEDLINE DUPLICATE 13

ACCESSION NUMBER: 1998058783 MEDLINE

DOCUMENT NUMBER: 98058783 PubMed ID: 9371814

TITLE: Heat shock fusion **proteins** as vehicles for **antigen** delivery into the major histocompatibility complex class I presentation pathway.

AUTHOR: Suzue K; Zhou X; Eisen H N; Young R A
CORPORATE SOURCE: Whitehead Institute for Biomedical Research, Cambridge, MA 02142, USA.
CONTRACT NUMBER: AI26463 (NIAID)
AI31869 (NIAID)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 Nov 25) 94 (24) 13146-51.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980122
Last Updated on STN: 19980122
Entered Medline: 19980108

AB Mice immunized with **heat shock proteins** (**hsps**) isolated from mouse tumor cells (donor cells) produce **CD8 cytotoxic T lymphocytes** (CTL) that recognize donor cell **peptides** in association with the major histocompatibility complex (MHC) class I **proteins** of the responding mouse. The CTL are induced apparently because **peptides** noncovalently associated with the isolated **hsp** molecules can enter the MHC class I **antigen** processing pathway of professional **antigen** -presenting cells. Using a recombinant heat shock fusion **protein** with a large fragment of ovalbumin covalently linked to mycobacterial **hsp70**, we show here that when the soluble fusion **protein** was injected without adjuvant into H-2b mice, CTL were produced that recognized an ovalbumin-derived **peptide**, SIINFEKL, in association with Kb. The **peptide** is known to arise from natural processing of ovalbumin in H-2b mouse cells, and CTL from the ovalbumin-**hsp70**-immunized mice and a highly effective CTL clone (4G3) raised against ovalbumin-expressing EL4 tumor cells (EG7-OVA) were equally effective in terms of the concentration of SIINFEKL required for half-maximal lysis in a CTL assay. The mice were also protected against lethal challenge with ovalbumin-expressing melanoma tumor cells. Because large **protein** fragments or whole **proteins** serving as fusion partners can be cleaved into short **peptides** in the MHC class I processing pathway, **hsp** fusion **proteins** of the type described here are promising candidates for vaccines aimed at eliciting **CD8** **CTL** in populations of MHC-disparate individuals.

L8 ANSWER 31 OF 45 MEDLINE
ACCESSION NUMBER: 1998026164 MEDLINE
DOCUMENT NUMBER: 98026164 PubMed ID: 9379042
TITLE: Intracytoplasmic delivery of listeriolysin O by a vaccinal strain of Bacillus anthracis induces CD8-mediated protection against Listeria monocytogenes.
AUTHOR: Sirard J C; Fayolle C; de Chastellier C; Mock M; Leclerc C; Berche P
CORPORATE SOURCE: Unite de Toxines et Pathogenie Bacteriennes, URA 1858 CNRS, Institut Pasteur, Paris, France.
SOURCE: JOURNAL OF IMMUNOLOGY, (1997 Nov 1) 159 (9) 4435-43.

Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971112

AB The facultative intracellular pathogen Listeria monocytogenes secretes a 58-kDa hemolysin, listeriolysin O (LLO), that allows bacteria to access the cytoplasm and to multiply inside infected cells. LLO is also a protective Ag required for the development of specific immunity. We studied the capacity of a new bacterial vector, derived from an attenuated strain of Bacillus anthracis, to deliver in vivo LLO and to induce protection against L. monocytogenes infection. The hly gene encoding LLO was fused to a B. anthracis regulatory region induced in vivo and was integrated into a resident plasmid of this bacterium. This recombinant strain secreted a functional LLO in vitro and inside phagosomes of bone marrow macrophages. This LLO production enabled the conversion of the extracellular replicating B. anthracis into an intracytoplasmic bacterium. LLO+ B. anthracis thus mimicked the intracellular behavior of L. monocytogenes in macrophages. Specific protection of mice against lethal doses of L. monocytogenes was induced by immunization with LLO+ B. anthracis. The immunity was mediated by CD8+ T lymphocytes and was associated with the activation of LLO-specific MHC class I-restricted **CD8+ CTL**, able to recognize the immunodominant H-2d-restricted epitope 91-99 of LLO. This study, therefore, suggests that intracytoplasmic delivery of LLO by B. anthracis is sufficient to induce a MHC class I-restricted CD8-mediated protection against L. monocytogenes. The LLO+ B. anthracis recombinant strain represents a potential vector for delivering foreign Ags involved in CD8-mediated protective responses.

L8 ANSWER 32 OF 45 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 97:114521 SCISEARCH
THE GENUINE ARTICLE: WE900
TITLE: Induction of cytotoxic T-Cell responses against culture filtrate **antigens** in Mycobacterium bovis bacillus Calmette-Guerin-infected mice
AUTHOR: Denis O; Lozes E; Huygen K (Reprint)
CORPORATE SOURCE: INST PASTEUR, LAB MYCOBACTERIAL IMMUNOL, ENGELANDSTR 642, B-1180 BRUSSELS, BELGIUM (Reprint); INST PASTEUR, LAB MYCOBACTERIAL IMMUNOL, B-1180 BRUSSELS, BELGIUM
COUNTRY OF AUTHOR: BELGIUM
SOURCE: INFECTION AND IMMUNITY, (FEB 1997) Vol. 65, No. 2, pp. 676-684.
Publisher: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW, WASHINGTON, DC 20005-4171.
ISSN: 0019-9567.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 61

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB CD8(+) T cells are essential for protection against mycobacteria, as is clearly demonstrated by the fatal outcome of experimental infection of beta-2 microglobulin knockout mice, However, the mechanisms and **antigens** (Ags) leading to CD8(+) T-cell activation and regulation have been poorly characterized, Here we show that, upon immunization of major histocompatibility complex (MHC)-congenic mice with Mycobacterium bovis bacillus Calmette-Guerin (BCG), a cytotoxic response against BCG culture filtrate (CF) Ags (CFAgs) is induced in H-2(b) and H-2(bxd) haplotypes but not in H-2(d) haplotype, This response is mediated by CD8(+) T cells and absolutely requires the activation of CD4(+) T cells and their secretion of interleukin 2. The lack of cytotoxic response in H-2(d) mice cannot be explained by impaired cytokine production or by a defect in Ag presentation by H-2(d) macrophages. Using the MHC class I mutant B6.C-H-2(bm13) mouse strain, we demonstrate that cytotoxic T lymphocytes (CTLs) recognize CFAgs exclusively in association with D-b molecules, These Ags are cross-reactive in mycobacteria, since BCG-induced CTLs also recognize macrophages pulsed with CF from Mycobacterium tuberculosis H37Rv and H37Ra and from two virulent strains of ill. bovis, Moreover, immunization with Mycobacterium kansasii induces CTLs able to lyse macrophages pulsed with BCG CF, Finally, we have found that these Ags can be characterized as hydrophilic **proteins**, since they do not bind to phenyl-Sepharose CL-IB, Our results indicate that MHC-linked genes exert a profound influence on the generation of **CD8**(+) **CTLs** following BCG vaccination.

L8 ANSWER 33 OF 45 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 97:382821 SCISEARCH
THE GENUINE ARTICLE: WY418
TITLE: Induction of **CD8**(+) **CTL** recognizing mycobacterial **peptides**
AUTHOR: Vordermeier H M (Reprint); Zhu X; Harris D P
CORPORATE SOURCE: HAMMERSMITH HOSP, MRC, TB & RELATED INFECT UNIT, CTR CLIN SCI, DUCANE RD, LONDON W12 0NN, ENGLAND (Reprint)
COUNTRY OF AUTHOR: ENGLAND
SOURCE: SCANDINAVIAN JOURNAL OF IMMUNOLOGY, (MAY 1997) Vol. 45, No. 5, pp. 521-526.
Publisher: BLACKWELL SCIENCE LTD, OSNEY MEAD, OXFORD, OXON, ENGLAND OX2 0EL.
ISSN: 0300-9475.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 43

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Mycobacterium tuberculosis is the single, most important cause of morbidity attributable to a single infectious organism. CD8(+) T cells play an important role in anti-tuberculous immune responses in both mice and humans. Data concerning the identity of mycobacterial **antigens** recognized by CD8(+) T cells is limited; consequently, few CTL epitopes have been characterized. The authors identified allele-specific (H-2(b and d)) MHC class I binding motifs in six prominent M. tuberculosis **protein antigens** (the 19 and 38kDa lipoglycoproteins and the 10, 16, 65 and 70 kDa

stress **proteins**). These predicted epitopes were tested for MHC binding as well as their ability to elicit **peptide** -specific CTL following in vivo priming. The authors were able to identify eight previously undescribed mycobacterial CTL epitopes by using spleen cells from **peptide**-immunized mice. In addition, CTL specific for at least one of these epitopes also recognized the naturally processed epitope presented on transfected EL4 target cells. These mycobacteria-derived CTL epitopes could be important for future analysis of the involvement of CD8(+) T cells in M. tuberculosis infection, pathogenesis and vaccine development.

L8 ANSWER 34 OF 45 MEDLINE
ACCESSION NUMBER: 97459311 MEDLINE
DOCUMENT NUMBER: 97459311 PubMed ID: 9314082
TITLE: Acquired immunity to an intracellular pathogen: immunologic recognition of L. monocytogenes-infected cells.
AUTHOR: Bouwer H G; Barry R A; Hinrichs D J
CORPORATE SOURCE: Earle A. Chiles Research Institute, Portland, Oregon, USA.. bouwera@ohsu.edu
CONTRACT NUMBER: AI23455 (NIAID)
SOURCE: IMMUNOLOGICAL REVIEWS, (1997 Aug) 158 137-46. Ref: 47
Journal code: 7702118. ISSN: 0105-2896.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980217
Last Updated on STN: 19980217
Entered Medline: 19980130

AB Listeria monocytogenes (L. monocytogenes) is a pathogenic bacterium, and subclinical infection in mice is utilized as a prototypic model to investigate the development and expression of acquired resistance to facultative intracellular organisms. A key virulence factor of L. monocytogenes is the hemolysin listeriolysin O (LLO), and BALB/c mice immunized with hemolysin-secreting strains of L. monocytogenes develop specific acquired resistance, while mice immunized with hemolysin-negative strains or non-viable preparations of L. monocytogenes do not develop a protective immune response. Adoptive transfer studies show that L. monocytogenes-immune CD8+ T cells mediate acquired resistance. The L. monocytogenes-immune CD8+ population is cytotoxic, and target cells infected with hemolysin-secreting strains of L. monocytogenes are lysed, while target cells infected with hemolysin-negative strains or non-viable preparations of L. monocytogenes are not lysed. MHC class Ia and Ib molecules present L. monocytogenes-derived **peptides**, and we have identified Qa-Ib, a T-region-encoded MHC class Ib molecule, as a restriction element for L. monocytogenes-specific **CD8** + **CTL**. MHC class Ib-restricted CTL are stimulated following infection with L. monocytogenes and are a significant component of the total MHC class I-restricted CTL population. These findings support the observation that cytoplasmic L. monocytogenes-derived **antigens** are endogenously processed and presented in association with MHC class Ia and Ib molecules to

CD8+ effector cells, and that both populations of effector cells contribute to the immune response to this intracellular pathogen.

L8 ANSWER 35 OF 45 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 97163435 MEDLINE
DOCUMENT NUMBER: 97163435 PubMed ID: 9010255
TITLE: Synthetic **peptides** based on Chlamydia trachomatis **antigens** identify cytotoxic T lymphocyte responses in subjects from a trachoma-endemic population.
AUTHOR: Holland M J; Conway D J; Blanchard T J; Mahdi O M; Bailey R L; Whittle H C; Mabey D C
CORPORATE SOURCE: Department of Clinical Sciences, London School of Hygiene and Tropical Medicine, UK.
SOURCE: CLINICAL AND EXPERIMENTAL IMMUNOLOGY, (1997 Jan) 107 (1) 44-9.
Journal code: 0057202. ISSN: 0009-9104.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970306
Last Updated on STN: 19970306
Entered Medline: 19970221

AB **CD8+ cytotoxic T lymphocytes** (CTL) recognize **peptide antigens** in the context of class I MHC **antigen** molecules. To identify **peptides** capable of eliciting anti-Chlamydia trachomatis CTL responses, 13 synthetic **peptides** conforming to human leucocyte **antigen** (HLA)-B8- or -B35-predicted binding motifs were synthesized using sequences based on C. trachomatis major outer membrane **protein** (MOMP) and **heat shock protein** 60 (hsp60). Two of 11 HLA-B35-predicted binding **peptides** were able to stabilize HLA-B35 in an in vitro binding assay. All **peptides** were tested in CTL assays using peripheral blood mononuclear cells (PBMC) isolated from 26 HLA-B8 or -B35 individuals resident in a trachoma-endemic community. Responses to MOMP and hsp60 **peptides** were identified in a minority of both HLA-B8 and -B35 individuals. Two of 12 HLA-B8 subjects responded to MOMP and 1/13 to hsp60 **peptides**. Responses in HLA-B35 subjects were similar, 1/13 subjects responding to MOMP and 2/13 to hsp60 **peptides**. CTL responses were observed only in children resolving current infection and in adults without scarring of the conjunctiva. These results suggest that anti-chlamydial CTL occur at low levels in peripheral blood, but may be important in the resolution of naturally acquired human ocular chlamydial infection.

OF 45 MEDLINE
96201608 MEDLINE
96201608 PubMed ID: 8613407
Peptide epitopes from noncytosolic Listeria monocytogenes can be presented by major histocompatibility complex class I molecules.
Zwickey H L; Potter T A
Department of Medicine, National Jewish Center for Immunology and Respiratory Medicine, Denver, CO

Searcher : Shears 308-4994

80206-2761, USA.
CONTRACT NUMBER: AI28115 (NIAID)
AI37905 (NIAID)
SOURCE: INFECTION AND IMMUNITY, (1996 May) 64 (5) 1870-2.
Journal code: 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199606
ENTRY DATE: Entered STN: 19960613
Last Updated on STN: 19960613
Entered Medline: 19960606

AB Listeria monocytogenes is an intracellular pathogen which escapes the phagosome and resides in the cytosol of the host cell. Using Listeria innocua and a mutant strain of L. monocytogenes (listeriolysin O negative), which do not enter the cytosol of the host cell, we demonstrate class I presentation of an epitope of p60, a **protein** secreted by L. monocytogenes, to a class I-restricted **CD8+ cytotoxic T lymphocyte** clone.

L8 ANSWER 37 OF 45 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 96373472 EMBASE
DOCUMENT NUMBER: 1996373472
TITLE: Immune regulation in the male genital tract.
AUTHOR: Witkin S.S.; Jeremias J.; Bongiovanni A.M.; Munoz M.G.
CORPORATE SOURCE: Department of Obstetrics/Gynecology, Cornell University Medical College, 515 East 71st Street,New York, NY 10021, United States
SOURCE: Infectious Disease in Obstetrics and Gynecology, (1996) 4/3 (131-135).
ISSN: 1064-7449 CODEN: IDOGEX
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
028 Urology and Nephrology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Spermatozoa are not produced until puberty, long after the establishment of tolerance to self-**antigens**. Therefore, sperm-specific **antigens** are immunogenic in men. Most men, however, do not produce antibodies to their own gametes. Development of mechanisms to prevent or limit autoimmune responses to spermatozoa were essential for preservation of reproductive capacity. Tight junctions between adjacent Sertoli cells, as part of the blood-testis barrier, prevent sperm-immune cell contact. In some portions of the genital tract this barrier is thin or incomplete. Immune mechanisms have evolved to actively suppress the autoimmune response to spermatozoa within the genital tract. Unlike in the circulation where CD4+ helper T lymphocytes predominate, **CD8 + suppressor/cytotoxic T lymphocytes** are the most prominant T cells in the epididymis and vas deferens. In addition, spermatozoa suppress pro-inflammatory lymphocyte immune responses, possibly by inducing production of anti-inflammatory cytokines. Antisperm antibody production is induced in the male genital tract when a local infection or disruption in the genital

tract physical harrier leads to an influx of CD4+ T cells. In response to induction of a productive immune response, two additional mechanisms downregulate humoral immunity within the genital tract. T lymphocytes possessing the .gamma..delta. form of the **antigen** receptor (.gamma..delta. T cells) are concentrated in the male genital tract and in semen. These cells become activated and proliferate in men with evidence of sperm autoimmunity. Activated .gamma..delta. T cells inhibit production of antibodies by activated B lymphocytes, thereby limiting antisperm antibody production. **Heat shock proteins** (**hsps**) are also present in semen in association with infection and antisperm antibody formation. **Hsp** gene transcription leads to inhibition of transcription of the genes coding for pro-inflammatory cytokines and, conversely, to activation of .gamma..delta. T cells. Activated .gamma..delta. T cells also promote **hsp** synthesis. The mechanisms to inhibit immunity to sperm may hinder effective immune elimination of microorganisms in the male genital tract.

L8 ANSWER 38 OF 45 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 95015897 MEDLINE
DOCUMENT NUMBER: 95015897 PubMed ID: 7523514
TITLE: Beta 2-microglobulin independent presentation of exogenously added foreign **peptide** and endogenous self-epitope by MHC class I alpha-chain to a cross-reactive **CD8+ CTL** clone.
AUTHOR: Zugel U; Schoel B; Kaufmann S H
CORPORATE SOURCE: Department of Immunology, University of Ulm, Germany.
SOURCE: JOURNAL OF IMMUNOLOGY, (1994 Nov 1) 153 (9) 4070-80. Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199411
ENTRY DATE: Entered STN: 19941222
Last Updated on STN: 19960129
Entered Medline: 19941123

AB CD8+ T cells recognize antigenic **peptides** in the context of MHC class I molecules that encompass two distinct **polypeptide** chains, the MHC-encoded alpha-chain and the non-MHC-encoded beta 2-microglobulin (beta 2-m). The beta 2-m is considered essential for the stability and function of the MHC class I **peptide** complex and, hence, for **peptide** presentation to CD8+ T cells. In this study, we describe **peptide** presentation by macrophages from beta 2-m-deficient mice to a **CD8+ CTL** clone tht cross-recognizes an H-2Db-restricted **peptide** of the mycobacterial **heat shock protein** 60 (hsp60) and a self-**peptide** presented by IFN-gamma-stressed macrophages. Specific lysis of stressed or hsp60 **peptide**-pulsed beta 2-m-/- macrophages was inhibited by the nucleoprotein **peptide** with high affinity to H-2Db. Brefeldin A, a known inhibitor of MHC class I processing, interfered with lysis of IFN-gamma-stressed, but not of hsp60 **peptide**-pulsed, beta 2-m-/- macrophages. The hsp60 **peptide** failed to stimulate surface expression of H-2Db in beta 2-m-/- macrophages, and slightly increased MHC class I expression in the transporter mutant cell line

RMA-S, as detected by cytofluorometry. We concLude that presentation of endogenously processed cytosolic epitopes and exogenously added foreign **peptides** by the MHC class I alpha-chain can occur independent from beta 2-m. Presumably, H-2Db **peptides**, but not H-2Kb **peptides**, have the capacity to induce and/or stabilize surface expression of a small number of MHC class I alpha-chains, and this low density is sufficient for recognition by **CD8**+ **CTL**, although it need not be detected by serologic means.

L8 ANSWER 39 OF 45 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 95104308 MEDLINE
DOCUMENT NUMBER: 95104308 PubMed ID: 7805744
TITLE: Elongated **peptides**, not the predicted nonapeptide stimulate a major histocompatibility complex class I-restricted cytotoxic T lymphocyte clone with specificity for a bacterial **heat shock protein**.
AUTHOR: Schoel B; Zugel U; Ruppert T; Kaufmann S H
CORPORATE SOURCE: Department of Immunology, University of Ulm, FRG.
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1994 Dec) 24 (12) 3161-9.
Journal code: 1273201. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199501
ENTRY DATE: Entered STN: 19950215
Last Updated on STN: 19950215
Entered Medline: 19950127

AB The **peptides** recognized by an H-2Db-restricted **CD8** **cytotoxic T lymphocyte** (CTL) clone which is specific for the 60-kDa mycobacterial **heat shock protein** (**hsp**) and cross-reacts with stressed host cells were characterized. None of the nonapeptides from hsp60 conforming to the H-2Db binding motif were able to sensitize target cells for lysis by this CTL clone. Sequence analysis of the stimulatory fraction from a trypsin digest of hsp60, together with synthetic **peptide** studies, defined a cluster of overlapping epitopes. Carboxy-terminal extension by at least one amino acid of the nonamer predicted to bind best to H-2Db was essential for CTL recognition. Two such elongated **peptides** , a 10-mer and a 12-mer stimulated the clone at similarly low concentrations in the 100 pM range. We assume that these two **peptides** comply best with the natural epitope. In contrast, the 11-mer was inactive. The stimulatory 10-mer bound to H-2Db with an efficacy similar to that of the nonapeptide corresponding to the H-2Db motif, as revealed by **peptide** induced major histocompatibility complex (MHC) surface expression on RMA-S cells and competitive blocking of epitope recognition by the nonamer. Binding of these carboxy-terminally extended **peptides** to the MHC groove can be explained by anchoring through the amino acid residue Asn in position 5 of the **peptide** and by intrusion of the hydrophobic carboxy-terminal Ala (10-mer) or Leu (12-mer), but not Gly (11-mer), into the hydrophobic pocket of the H-2Db cleft. Because the carboxy-terminal part is thus larger than predicted, this region of the **peptide** may arch up from the

binding groove. We assume that recognition of steric components of the MHC/**peptide** complex broaden the range of epitope specificity for a single T cell receptor. This flexibility not only promotes recognition of several overlapping **peptides** from a single **antigen**, but may also increase the chance of cross-reaction with similar **peptides** from unrelated **proteins**, including autoantigens. Consistent with this latter assumption, the T cell clone cross-recognizes mycobacterial hsp60 and stressed host cells.

L8 ANSWER 40 OF 45 MEDLINE
ACCESSION NUMBER: 95053755 MEDLINE
DOCUMENT NUMBER: 95053755 PubMed ID: 7964496
TITLE: Delivery of a viral **antigen** to the class I processing and presentation pathway by Listeria monocytogenes.
AUTHOR: Ikonomidis G; Paterson Y; Kos F J; Portnoy D A
CORPORATE SOURCE: Department of Microbiology, University of Pennsylvania School of Medicine, Philadelphia 19104-6076.
CONTRACT NUMBER: AI-27655 (NIAID)
GM-31841 (NIGMS)
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1994 Dec 1) 180 (6) 2209-18.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199412
ENTRY DATE: Entered STN: 19950110
Last Updated on STN: 19970203
Entered Medline: 19941223

AB Listeria monocytogenes is a facultative intracellular pathogen that grows in the cytoplasm of infected host cells. We examined the capacity of L. monocytogenes to introduce influenza nucleoprotein (NP) into the class I pathway of **antigen** presentation both in vitro and in vivo. Recombinant L. monocytogenes secreting a fusion of listeriolysin O and NP (LLO-NP) targeted infected cells for lysis by NP-specific class I-restricted cytotoxic T cells. **Antigen** presentation occurred in the context of three different class I haplotypes in vitro. A hemolysin-negative L. monocytogenes strain expressing LLO-NP was able to present in a class II-restricted manner. However, it failed to target infected cells for lysis by CD8+ T cells, indicating that hemolysin-dependent bacterial escape from the vacuole is necessary for class I presentation in vitro. Immunization of mice with a recombinant L. monocytogenes strain that stably expressed and secreted LLO-NP induced NP-specific **CD8+ cytotoxic T lymphocytes**. These studies have implications for the use of L. monocytogenes to deliver potentially any **antigen** to the class I pathway in vivo.

L8 ANSWER 41 OF 45 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 94:451295 SCISEARCH
THE GENUINE ARTICLE: NX261
TITLE: **PEPTIDE** TRANSPORTER-INDEPENDENT, STRESS **PROTEIN**-MEDIATED ENDOSOMAL PROCESSING OF

ENDOGENOUS **PROTEIN ANTIGENS** FOR MAJOR HISTOCOMPATIBILITY COMPLEX CLASS-I PRESENTATION

AUTHOR: SCHIRMBECK R; REIMANN J (Reprint)
CORPORATE SOURCE: UNIV ULM, INST MICROBIOL, ALBERT EINSTEIN ALLEE 11, D-89069 ULM, GERMANY (Reprint); UNIV ULM, INST MICROBIOL, D-89069 ULM, GERMANY
COUNTRY OF AUTHOR: GERMANY
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (JUL 1994) Vol. 24, No. 7, pp. 1478-1486.
ISSN: 0014-2980.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 78

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The **peptide** transporter-defective cell line RMA-S expressing the wild-type simian virus 40 large T **antigen** (wtT-Ag) from a transfected gene did not present two well-defined, H-2 class I (D-b)-restricted epitopes of T-Ag to cytotoxic T lymphocytes (CTL). Hence, ''endogenous'' processing and presentation of the wtT-Ag depended on a functional **peptide** transporter heterodimer. In contrast, both T-Ag epitopes were efficiently presented to CTL by transfected RMA-S cells expressing a truncated, cytoplasmic T-Ag variant (cT-Ag) or a karyophilic, amino-terminal 272-amino acid T-Ag fragment. Transporter-independent ''endogenous'' processing of mutant T-Ag molecules correlated with their association with the constitutively expressed **heat shock protein** 73 (hsp73). Class I-restricted presentation of both epitopes processed from these hsp73-associated **protein antigens** was sensitive to NH4Cl and chloroquine. These data indicate that selected intracellular **proteins** access an alternative, hsp73-mediated pathway for class I-restricted presentation that operates independent of **peptide** transporters in an endosomal compartment.

L8 ANSWER 42 OF 45 MEDLINE

ACCESSION NUMBER: 94298843 MEDLINE
DOCUMENT NUMBER: 94298843 PubMed ID: 8026511
TITLE: Presentation of Listeria monocytogenes **antigens** by major histocompatibility complex class I molecules to **CD8 cytotoxic T lymphocytes** independent of listeriolysin secretion and virulence.
AUTHOR: Szalay G; Hess J; Kaufmann S H
CORPORATE SOURCE: Department of Immunology, University of Ulm, FRG.
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1994 Jul) 24 (7) 1471-7.
Journal code: 1273201. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199408
ENTRY DATE: Entered STN: 19940818
Last Updated on STN: 19940818
Entered Medline: 19940809

AB Virulence and intracellular persistence of Listeria monocytogenes

markedly depend on secretion of listeriolysin (Hly), which promotes invasion of the pathogen from the endosome into the cytosol. Recent studies have provided compelling evidence that Hly also facilitates recognition of listerial **antigens**, in association with major histocompatibility complex (MHC) class I molecules, by CD8 T lymphocytes. Data presented here confirm that the Hly-deficient strains, the prfA- mutant L. monocytogenes SLCC53 and the transposon mutants L. monocytogenes M3 and M20 are avirulent for mice, and unable to replicate inside bone marrow-derived macrophages (BMM phi). Furthermore, BMM phi infected with M3, M20 or SLCC53 were as efficiently lysed as BMM phi infected with the Hly-positive wild-type strain EGD by MHC class I-dependent **CD8 cytotoxic T lymphocytes**. Using the highly sensitive polymerase chain reaction method, hly mRNA was detectable in BMM phi infected with L. monocytogenes EGD or SLCC53, but totally absent in M3-infected BMM phi. In the case of M20, an excision of the transposon occurred, but the excision was not precise and the hly gene was approximately 400 base pairs shorter. These findings argue against a unique role for Hly in MHC class I presentation of listerial **antigens**, although Hly appears central to virulence and intracellular replication. Thus, virulence of L. monocytogenes is dissociable from MHC class I presentation of listerial **antigens**.

L8 ANSWER 43 OF 45 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 93105395 MEDLINE
DOCUMENT NUMBER: 93105395 PubMed ID: 8093229
TITLE: Autoreactive and **heat shock protein** 60-recognizing CD4+ T-cells show antitumor activity against syngeneic fibrosarcoma.
AUTHOR: Harada M; Matsuzaki G; Yoshikai Y; Kobayashi N; Kurosawa S; Takimoto H; Nomoto K
CORPORATE SOURCE: Department of Immunology, Kyushu University, Fukuoka, Japan.
SOURCE: CANCER RESEARCH, (1993 Jan 1) 53 (1) 106-11. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199301
ENTRY DATE: Entered STN: 19930212
Last Updated on STN: 19950206
Entered Medline: 19930125

AB A CD4+ **heat shock protein** (**hsp**) 60-recognizing autoreactive T-cell line (BASL1) and clone (BASL1.1) were examined for their antitumor activity against major histocompatibility complex class II- syngeneic Meth A fibrosarcoma (Meth A), which was immunofluorescently stained with monoclonal antibody specific for **hsp** 60. In in vitro proliferative assay, BASL1.1 was suggested to recognize Meth A-derived **hsp** 60 presented by syngeneic **antigen**-presenting cells in a major histocompatibility complex class II-restricted manner. This cell line and clone showed antitumor activity in tumor-neutralizing (Winn) assay. BASL1 and BASL1.1 cells produced gamma-interferon, tumor necrosis factor, and interleukin 2 but not interleukin 4 by the stimulation with syngeneic spleen cells. In cytolytic assay, these cell lines and clones showed neither direct nor indirect

(bystander) cytolysis against Meth A. In cytostatic assay, these cells inhibited the proliferation of Meth A in the presence of syngeneic macrophages, and this activity was abrogated by the addition of anti-gamma-interferon monoclonal antibody. Recombinant gamma-interferon could induce cytostatic activity only in the presence of macrophages, and tumor necrosis factor synergized this activity. Antitumor activity induced by BASL1 was abrogated by the administration of anti-CD8 monoclonal antibody in vivo, suggesting that **CD8+ cytotoxic T-lymphocytes** are essential and final effector cells for BASL1-mediated Meth A rejection. These findings indicate that CD4+ autoreactive and **hsp** 60-recognizing T-cells show two types of antitumor activity: cytostasis and induction of tumor-specific cytotoxic T-lymphocytes. Furthermore, these results imply that tumor-specific immunity could be elicited by CD4+ helper T-cells which recognize **hsp**.

L8 ANSWER 44 OF 45 MEDLINE
ACCESSION NUMBER: 92105754 MEDLINE
DOCUMENT NUMBER: 92105754 PubMed ID: 1729372
TITLE: Metabolic requirements for macrophage presentation of Listeria monocytogenes to immune CD8 cells.
AUTHOR: Brown M L; Fields P E; Kurlander R J
CORPORATE SOURCE: Department of Medicine, Duke University Medical Center, Durham, NC 27710.
CONTRACT NUMBER: PO1-AI123308 (NIAID)
RO1-AI18073 (NIAID)
SOURCE: JOURNAL OF IMMUNOLOGY, (1992 Jan 15) 148 (2) 555-61.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199202
ENTRY DATE: Entered STN: 19920302
Last Updated on STN: 19920302
Entered Medline: 19920211

AB Though ingested Ag are readily degraded into **peptides** within endocytic vesicles, APC usually cannot present these fragments to CD8 cells. Despite this generalization, some exceptions have been noted. For example, murine macrophage targets readily process heat-killed Listeria monocytogenes (HKLM) into a form recognizable by immune **CD8 CTL**. Using an assay of Listeria-specific, CD8-mediated cytotoxicity to quantitate Ag presentation by C57Bl/6 macrophage targets, we have examined some of the cellular requirements for this form of Ag processing. To assess whether the physical form of the Ag is an important determinant of processing, we compared the ability of macrophages to present intact HKLM, fractionated L. monocytogenes (LM) membranes, and octyl-beta-d-thioglucopyranoside-solubilized extracts of LM membranes. Macrophages presented each Ag form in a similar manner indicating that processing is not critically dependent on the presence of intact bacteria or even on the introduction of Ag in a particulate form. To gain insight into the metabolic requirements for Ag processing, we examined the effects of several inhibitors. As might be expected, listerial Ag presentation was blocked by brefeldin, a known inhibitor of the endogenous pathway of Ag processing. LM Ag presentation, however, was also blocked by

```
=> "heat shock protein"
L1       31771 "HEAT SHOCK PROTEIN"

=> "amino acid substitution"
L2       21250 "AMINO ACID SUBSTITUTION"

=> L1 and L2
L3          86 L1 AND L2

=> "complex" or "fusion protein" and L3
L4     1762302 "COMPLEX" OR "FUSION PROTEIN" AND L3

=> fusion and L3
L5          10 FUSION AND L3

=> "ATP binding domain" and L3
L6           0 "ATP BINDING DOMAIN" AND L3

=> conjugation and L3
L7           0 CONJUGATION AND L3

=> joined and L3
L8           0 JOINED AND L3

=> mix and L3
L9           0 MIX AND L3

=> D L5 IBIB TI SO AU ABS 1-10

L5   ANSWER 1 OF 10  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:        2000:376244  CAPLUS
DOCUMENT NUMBER:         133:147758
TITLE:                   A transmembrane guanylyl cyclase (DAF-11) and Hsp90
                         (DAF-21) regulate a common set of chemosensory
                         behaviors in Caenorhabditis elegans
AUTHOR(S):               Birnby, Deborah A.; Link, Elizabeth Malone; Vowels,
                         Jennifer J.; Tian, Hong; Colacurcio, Patrick L.;
                         Thomas, James H.
CORPORATE SOURCE:        Department of Genetics, University of Washington,
                         Seattle, WA, 98195-7360, USA
SOURCE:                  Genetics (2000), 155(1), 85-104
                         CODEN: GENTAE; ISSN: 0016-6731
PUBLISHER:               Genetics Society of America
DOCUMENT TYPE:           Journal
LANGUAGE:                English
TI   A transmembrane guanylyl cyclase (DAF-11) and Hsp90 (DAF-21) regulate a
     common set of chemosensory behaviors in Caenorhabditis elegans
SO   Genetics (2000), 155(1), 85-104
     CODEN: GENTAE; ISSN: 0016-6731
AU   Birnby, Deborah A.; Link, Elizabeth Malone; Vowels, Jennifer J.; Tian,
     Hong; Colacurcio, Patrick L.; Thomas, James H.
AB   C. elegans daf-11 and daf-21 mutants share defects in specific
     chemosensory responses mediated by several classes of sensory neurons,
     indicating that these 2 genes have closely related functions in an
     assortment of chemosensory pathways.  We report that daf-11 encodes 1 of
a
     large family of C. elegans transmembrane guanylyl cyclases (TM-GCs).  The
     cGMP analog 8-bromo-cGMP rescues a sensory defect in both daf-11 and
     daf-21 mutants, supporting a role for DAF-11 guanylyl cyclase activity in
     this process and further suggesting that daf-21 acts at a similar step.
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Daf-11 :: gfp **fusions** are expressed in 5 identified pairs of chemosensory neurons in a pattern consistent with most daf-11 mutant phenotypes. We also show that daf-21 encodes the **heat-shock protein** 90 (Hsp90), a chaperone with numerous specific protein targets. The viable chemosensory-deficient daf-21 mutation is an unusual allele resulting from a single **amino acid substitution** and that the daf-21 null phenotype is early larval lethality. These results demonstrate that cGMP is a prominent 2nd messenger in C. elegans chemosensory transduction and suggest a previously unknown role for Hsp90 in regulating cGMP levels.

REFERENCE COUNT: 100 THERE ARE 100 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:336139 CAPLUS
DOCUMENT NUMBER: 133:100967
TITLE: Hyperactive forms of the Pdr1p transcription factor fail to respond to positive regulation by the Hsp70 protein Pdr13p
AUTHOR(S): Hallstrom, Timothy C.; Moye-Rowley, W. Scott
CORPORATE SOURCE: Molecular Biology Program, University of Iowa, Iowa City, IA, 52242, USA
SOURCE: Molecular Microbiology (2000), 36(2), 402-413
CODEN: MOMIEE; ISSN: 0950-382X
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Hyperactive forms of the Pdr1p transcription factor fail to respond to positive regulation by the Hsp70 protein Pdr13p
SO Molecular Microbiology (2000), 36(2), 402-413
CODEN: MOMIEE; ISSN: 0950-382X
AU Hallstrom, Timothy C.; Moye-Rowley, W. Scott
AB Multidrug resistance in Saccharomyces cerevisiae is commonly assocd. with the overprodn. of ATP-binding cassette transporter proteins such as Pdr5p or Yor1p. The Cys6-Zn(II)2 cluster-contg. transcription factors Pdr1p and Pdr3p are key regulators of expression of these pleiotropic drug resistance (PDR) loci. Previous expts. have demonstrated that the Hsp70 protein encoded by the PDR13 gene is a pos. regulator of Pdr1p function. We have examd. the mechanism underlying the control of Pdr1p by Pdr13p. Expression of deletion, insertion and **amino acid substitution** mutant variants of Pdr1p suggest that the center region of the transcription factor is the target for Pdr13p-mediated pos. regulation. Immunol. and **fusion** protein analyses demonstrate that Pdr13p is located in the cytoplasm, while Pdr1p is found in the nucleus. Biochem. fractionation expts. indicate that Pdr13p is assocd. with a high-mol.-wt. complex and suggest the assocn. of some fraction of Pdr13p with ribosomes.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:904277 CAPLUS
DOCUMENT NUMBER: 124:168550
TITLE: Mechanism of dimer formation of the 90-kDa **heat-shock protein**
AUTHOR(S): Nemoto, Takayuki; Ohara-Nemoto, Yuko; Ota, Minoru;

Takagi, Takashi; Yokoyama, Kazushige
CORPORATE SOURCE: Dep. Biochem., Iwate Med. Univ. Sch. Dentistry, Morioka, Japan
SOURCE: European Journal of Biochemistry (1995), 233(1), 1-8
CODEN: EJBCAI; ISSN: 0014-2956
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
TI Mechanism of dimer formation of the 90-kDa **heat-shock protein**
SO European Journal of Biochemistry (1995), 233(1), 1-8
CODEN: EJBCAI; ISSN: 0014-2956
AU Nemoto, Takayuki; Ohara-Nemoto, Yuko; Ota, Minoru; Takagi, Takashi; Yokoyama, Kazushige
AB Mechanism of homodimer formation of the 90-kDa **heat-shock protein** (HSP90) is described. In eukaryotic cells, there are 2 HSP90 isoforms, .alpha. and .beta., encoded by 2 sep. genes. HSP90.alpha. exists predominantly as a homodimer, HSP90.beta. mainly as a monomer. Anal. by native PAGE revealed that bacterially expressed HSP90.alpha. fused to glutathione S-transferase (GST) existed as a high-mol.-mass oligomer, and was converted to a homodimer following removal of the **fusion** enzyme by thrombin cleavage. A deletion mutant, HSP90.alpha.D44-603, formed a monomer and an N-terminal truncated mutant, HSP90.alpha.533-732, existed as a dimer, indicating that the dimer-forming ability resides somewhere in the C-terminal 200 amino acids.
Limited proteolysis of the C-terminal 200 amino acids of HSP90.alpha. with chymotrypsin produced the C-terminal 16-kDa fragment (Met628/Ala629-Asp732) and its adjacent more N-terminal 13-kDa fragment (Val542-Tyr627/Met628). Size-exclusion HPLC and 2-dimensional PAGE analyses demonstrated that these 2 chymotryptic fragments bound each other. The C-terminal 198 amino acids as well as the full-length form of HSP90.beta. revealed a lower dimer-forming activity than HSP90.alpha.. Expression of the chimeric proteins at the C-terminal 198 amino acids of the .alpha. and .beta. isoforms further indicated that the 16 **amino acid substitutions** locating between amino acids 561 and 685 account for the impeded dimerization of HSP90.beta.. A Leu zipper motif (Met402-Leu423) was unlikely to be involved in the dimer formation. Taken together, these results indicate that the dimeric structure of HSP90.alpha. is mediated by the C-terminal 191 amino acids and consists of duplicate interactions of the C-terminal region (Met628/Ala629-Asp732) of one subunit and the adjacent more N-terminal region (Val542-Try627/Met628) of the other subunit.

L5 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:361939 CAPLUS
DOCUMENT NUMBER: 123:26827
TITLE: Construction of recombinant Neisserial Hsp60 proteins and mapping of antigenic domains
AUTHOR(S): Pannekoek, Yvonne; Dankert, Jacob; van Putten, Jos P. M.
CORPORATE SOURCE: Abteilung Infektionsbiologie, Max-Planck-Institut Biologie, Tuebingen, D-72076, Germany
SOURCE: Molecular Microbiology (1995), 15(2), 277-85
CODEN: MOMIEE; ISSN: 0950-382X
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Construction of recombinant Neisserial Hsp60 proteins and mapping of antigenic domains
SO Molecular Microbiology (1995), 15(2), 277-85
CODEN: MOMIEE; ISSN: 0950-382X
AU Pannekoek, Yvonne; Dankert, Jacob; van Putten, Jos P. M.
AB The cloning and expression is reported of PCR-amplified DNA encoding the 63-kDa stress-inducible protein of Neisseria gonorrhoeae strains VP1 and PID2, Neisseria meningitidis 2996 and the commensal Neisseria flavescens. DNA sequence anal. revealed in all cases one open reading frame of 541-544 amino acids corresponding to a protein of approx. 57,000 Da. The various neisserial proteins were >96% identical at the amino acid level and showed extensive homol. with proteins belonging to the Hsp60 **heat-shock-protein** family. The authors constructed defined glutathione S-transferase **fusion** polypeptides of the gonococcal Hsp60 homolog to locate antigenic domains on the recombinant protein. Variation in the immunoreactivity of two monoclonal antibodies recognizing a conserved and a Neisseria-unique antigenic Hsp60 determinant, resp., could thus be deduced to result from single **amino acid substitutions**. Anal. of the antibody response in patients' sera demonstrated reactivity with the same **fusion** polypeptides in six out of nine sera, indicating that neisserial Hsp60 is expressed during the natural infection and that distinct domains on the protein are immunodominant in vivo.

L5 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1987:208621 CAPLUS
DOCUMENT NUMBER: 106:208621
TITLE: The use of operon **fusions** in studies of the heat-shock response: effects of altered sigma 32 on heat-shock promoter function in Escherichia coli
AUTHOR(S): Yano, Ryoji; Imai, Mutsuo; Yura, Takashi
CORPORATE SOURCE: Inst. Virus Res., Kyoto Univ., Kyoto, 606, Japan
SOURCE: Molecular and General Genetics (1987), 207(1), 24-8
CODEN: MGGEAE; ISSN: 0026-8925
DOCUMENT TYPE: Journal
LANGUAGE: English
TI The use of operon **fusions** in studies of the heat-shock response: effects of altered sigma 32 on heat-shock promoter function in Escherichia coli
SO Molecular and General Genetics (1987), 207(1), 24-8
CODEN: MGGEAE; ISSN: 0026-8925
AU Yano, Ryoji; Imai, Mutsuo; Yura, Takashi
AB Derivs. of .lambda.pF13 phage in which lacZ expression (.beta.-galactosidase synthesis) is directed by transcription initiated at a heat-shock promoter (PropoDhs or PgroE) were constructed and used for anal. of the heat-shock response in E. coli. A wild-type strain (MC4100) lysogenic for either of these phages exhibited typical transient induction of .beta.-galactosidase synthesis upon a temp. shift from 30.degree. to 42.degree. or after addn. of ethanol to the medium (4% to 5%) at 30.degree.. In contrast, most amber rpoH (htpR) mutants tested (in a Su- background) failed to respond to a temp. shift, though some mutants affected in the carboxy-terminal region exhibited a partial response. All

rpoH mutants tested showed a weak but significant response to ethanol. F' plasmids carrying each of 6 known nonsense suppressors were then introduced into each of 4 rpoH amber mutants lysogenic for .lambda.pF13-(Phs-lacZ), creating a set of F' strains that produce sigma 32 protein with a specific **amino acid substitution** at a known site. Some of these strains showed an essentially normal heat-shock response, while others showed little response with either or both of the promoters. In some instances, the response was significantly delayed. These results point to the usefulness of the .lambda.pF13-deriv. phages for quant. and systematic anal. of heat-shock response in E. coli.

L5 ANSWER 6 OF 10 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:266407 BIOSIS
DOCUMENT NUMBER: PREV200000266407
TITLE: Hyperactive forms of the Pdr1p transcription factor fail to respond to positive regulation by the Hsp70 protein Pdr13p.
AUTHOR(S): Hallstrom, Timothy C.; Moye-Rowley, W. Scott (1)
CORPORATE SOURCE: (1) Molecular Biology Program, University of Iowa, 5-430 Bowen Science Building, Iowa City, IA, 52242 USA
SOURCE: Molecular Microbiology, (April, 2000) Vol. 36, No. 2, pp. 402-413. print..
ISSN: 0950-382X.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
TI Hyperactive forms of the Pdr1p transcription factor fail to respond to positive regulation by the Hsp70 protein Pdr13p.
SO Molecular Microbiology, (April, 2000) Vol. 36, No. 2, pp. 402-413. print..
ISSN: 0950-382X.
AU Hallstrom, Timothy C.; Moye-Rowley, W. Scott (1)
AB Multidrug resistance in Saccharomyces cerevisiae is commonly associated with the overproduction of ATP-binding cassette transporter proteins such as Pdr5p or Yor1p. The Cys6-Zn(II)2 cluster-containing transcription factors Pdr1p and Pdr3p are key regulators of expression of these pleiotropic drug resistance (PDR) loci. Previous experiments have demonstrated that the Hsp70 protein encoded by the PDR13 gene is a positive regulator of Pdr1p function. We have examined the mechanism underlying the control of Pdr1p by Pdr13p. Expression of deletion, insertion and **amino acid substitution** mutant variants of Pdr1p suggest that the centre region of the transcription factor is the target for Pdr13p-mediated positive regulation. Immunological and **fusion** protein analyses demonstrate that Pdr13p is located in the cytoplasm, while Pdr1p is found in the nucleus. Biochemical fractionation experiments indicate that Pdr13p is associated with a high-molecular-weight complex and suggest the association of some fraction of Pdr13p with ribosomes.

L5 ANSWER 7 OF 10 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:254319 BIOSIS
DOCUMENT NUMBER: PREV200000254319
TITLE: A transmembrane guanylyl cyclase (DAF-11) and Hsp90 (DAF-21) regulate a common set of chemosensory behaviors in Caenorhabditis elegans.

AUTHOR(S): Birnby, Deborah A.; Malone Link, Elizabeth; Vowels, Jennifer J.; Tian, Hong; Colacurcio, Patrick L.; Thomas, James H. (1)
CORPORATE SOURCE: (1) Department of Genetics, University of Washington, Seattle, WA, 98195-7360 USA
SOURCE: Genetics, (May, 2000) Vol. 155, No. 1, pp. 85-104. print..
ISSN: 0016-6731.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
TI A transmembrane guanylyl cyclase (DAF-11) and Hsp90 (DAF-21) regulate a common set of chemosensory behaviors in Caenorhabditis elegans.
SO Genetics, (May, 2000) Vol. 155, No. 1, pp. 85-104. print..
ISSN: 0016-6731.
AU Birnby, Deborah A.; Malone Link, Elizabeth; Vowels, Jennifer J.; Tian, Hong; Colacurcio, Patrick L.; Thomas, James H. (1)
AB Caenorhabditis elegans daf-11 and daf-21 mutants share defects in specific chemosensory responses mediated by several classes of sensory neurons, indicating that these two genes have closely related functions in an assortment of chemosensory pathways. We report that daf-11 encodes one of a large family of C. elegans transmembrane guanylyl cyclases (TM-GCs). The cyclic GMP analogue 8-bromo-cGMP rescues a sensory defect in both daf-11 and daf-21 mutants, supporting a role for DAF-11 guanylyl cyclase activity in this process and further suggesting that daf-21 acts at a similar step. daf-11::gfp **fusions** are expressed in five identified pairs of chemosensory neurons in a pattern consistent with most daf-11 mutant phenotypes. We also show that daf-21 encodes the **heat-shock protein** 90 (Hsp90), a chaperone with numerous specific protein targets. We show that the viable chemosensory-deficient daf-21 mutation is an unusual allele resulting from a single **amino acid substitution** and that the daf-21 null phenotype is early larval lethality. These results demonstrate that cGMP is a prominent second messenger in C. elegans chemosensory transduction and suggest a previously unknown role for Hsp90 in regulating cGMP levels.

L5 ANSWER 8 OF 10 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:462498 BIOSIS
DOCUMENT NUMBER: PREV199699184854
TITLE: A new member of the hsp90 family of molecular chaperones interacts with the retinoblastoma protein during mitosis and after heat shock.
AUTHOR(S): Chen, Chi-Fen; Chen, Yumay; Dai, Kang; Chen, Phang-Lang; Riley, Daniel J.; Lee, Wen-Hwa (1)
CORPORATE SOURCE: (1) Cent. Mol. Med./Inst. Biotechnol., Univ. Texas Health Sci. Cent. San Antonio, 15355 Lambda Dr., San Antonio, TX 78245 USA
SOURCE: Molecular and Cellular Biology, (1996) Vol. 16, No. 9, pp. 4691-4699.
ISSN: 0270-7306.
DOCUMENT TYPE: Article
LANGUAGE: English
TI A new member of the hsp90 family of molecular chaperones interacts with the retinoblastoma protein during mitosis and after heat shock.
SO Molecular and Cellular Biology, (1996) Vol. 16, No. 9, pp. 4691-4699.

ISSN: 0270-7306.
AU Chen, Chi-Fen; Chen, Yumay; Dai, Kang; Chen, Phang-Lang; Riley, Daniel J.;
Lee, Wen-Hwa (1)
AB A gene encoding a new **heat shock protein** that may function as a molecular chaperone for the retinoblastoma protein (Rb) was characterized. The cDNA fragment was isolated by using the yeast two-hybrid system and Rb as bait. The open reading frame of the longest cDNA codes for a protein with substantial sequence homology to members of the hsp90 family. Antibodies prepared against **fusions** between glutathione S-transferase and portions of this new **heat shock protein** specifically recognized a 75-kDa cellular protein, hereafter designated hsp75, which is expressed ubiquitously and located in the cytoplasm. A unique LxCxE motif in hsp75, but not in other hsp90 family members', appears to be important for binding to the simian virus 40 T-antigen-binding domain of hypophosphorylated Rb, since a single mutation changing the cysteine to methionine abolishes the binding. In mammalian cells, Rb formed complexes with hsp75 under two special physiological conditions: (i) during M phase, when the envelope that separates the nuclear and cytoplasmic compartments broke down, and (ii) after heat shock, when hsp75 moved from its normal cytoplasmic location into the nucleus. In vitro, hsp75 had a biochemical activity to refold denatured Rb into its native conformation. Taken together, these results suggest that Rb may be a physiological substrate for the hsp75 chaperone molecule. The discovery of a **heat shock protein** that chaperones Rb identifies a mechanism, in addition to phosphorylation, by which Rb is regulated in response to progression of the cell cycle and to external stimuli.

L5 ANSWER 9 OF 10 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:21092 BIOSIS
DOCUMENT NUMBER: PREV199698593227
TITLE: Mechanism of dimer formation of the 90-kDa **heat-shock protein**.
AUTHOR(S): Nemoto, Takayuki (1); Ohara-Nemoto, Yuko; Ota, Minoru; Takagi, Takashi; Yokoyama, Kazushige
CORPORATE SOURCE: (1) Dep. Biochem., Iwate Med. Univ. Sch. Dent., 19-1 Uchimaru, Morioka 020 Japan
SOURCE: European Journal of Biochemistry, (1995) Vol. 233, No. 1, pp. 1-8.
ISSN: 0014-2956.
DOCUMENT TYPE: Article
LANGUAGE: English
TI Mechanism of dimer formation of the 90-kDa **heat-shock protein**.
SO European Journal of Biochemistry, (1995) Vol. 233, No. 1, pp. 1-8.
ISSN: 0014-2956.
AU Nemoto, Takayuki (1); Ohara-Nemoto, Yuko; Ota, Minoru; Takagi, Takashi; Yokoyama, Kazushige
AB This study describes the mechanism of homodimer formation of the 90-kDa **heat-shock protein** (HSP90). In eukaryotic cells, there are two HSP90 isoforms, alpha and beta, encoded by two separate genes. HSP90-alpha exists predominantly as a homodimer. HSP90-beta mainly as a monomer. Analysis by native PAGE revealed that bacterially expressed HSP90-alpha fused to glutathione S-transferase (GST) existed as a high-molecular-mass oligomer, and was converted to a homodimer following removal of the **fusion** enzyme by thrombin cleavage. A deletion mutant, HSP90-alpha-D44-603, formed a monomer and an

N-terminal truncated mutant, HSP90-alpha-533-732, existed as a dimer, indicating that the dimer-forming ability resides somewhere in the C-terminal 200 amino acids. Limited proteolysis of the C-terminal 200 amino acids of HSP90-alpha with chymotrypsin produced the C-terminal 16-kDa fragment (Met628/Ala629-Asp732) and its adjacent more N-terminal 13-kDa fragment (Val542-Tyr627/Met628). Size-exclusion HPLC and two-dimensional PAGE analyses demonstrated that these two chymotryptic fragments bound each other. The C-terminal 198 amino acids as well as the full-length form of HSP90-beta revealed a lower dimer-forming activity than HSP90-alpha. Expression of the chimeric proteins at the C-terminal 198 amino acids of the alpha and beta isoforms further indicated that the 16 **amino acid substitutions** locating between amino acids 561 and 685 account for the impeded dimerization of HSP90-beta. A leucine zipper motif (Met402-Leu423) was unlikely to be involved in the dimer formation. Taken together, these results indicate that the dimeric structure of HSP90-alpha is mediated by the C-terminal 191 amino acids and consists of duplicate interactions of the C-terminal region (Met628/Ala629-Asp732) of one subunit and the adjacent more N-terminal region (Val542-Try627/Met628) of the other subunit.

L5 ANSWER 10 OF 10 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1995:125481 BIOSIS
DOCUMENT NUMBER: PREV199598139781
TITLE: Construction of recombinant neisserial Hsp60 proteins and mapping of antigenic domains.
AUTHOR(S): Pannekoek, Yvonne; Dankert, Jacob; Van Putten, Jos P. M. (1)
CORPORATE SOURCE: (1) Max-Planck-Inst. Biol., Abt. Infektionsbiol., Spemannstrasse 34, D-72076 Tuebingen Germany
SOURCE: Molecular Microbiology, (1995) Vol. 15, No. 2, pp. 277-285.
ISSN: 0950-382X.
DOCUMENT TYPE: Article
LANGUAGE: English
TI Construction of recombinant neisserial Hsp60 proteins and mapping of antigenic domains.
SO Molecular Microbiology, (1995) Vol. 15, No. 2, pp. 277-285.
ISSN: 0950-382X.
AU Pannekoek, Yvonne; Dankert, Jacob; Van Putten, Jos P. M. (1)
AB Here we report the cloning and expression, in Escherichia coli, of PCR-amplified DNA encoding the 63-kDa stress-inducible protein of Neisseria gonorrhoeae strains VP1 and PID2, Neisseria meningitidis 2996 and the commensal Neisseria flavescens. DNA sequence analysis revealed in all cases one open reading frame of 541-544 amino acids corresponding to a protein of approximately 57 000 Da. The various neisserial proteins were gt 96% identical at the amino acid level and showed extensive homology with proteins belonging to the Hsp60 **heat-shock-protein** family. We constructed defined glutathione S-transferase **fusion** polypeptides of the gonococcal Hsp60 homologue to locate antigenic domains on the recombinant protein. Variation in the immunoreactivity of two monoclonal antibodies recognizing a conserved and a neisseria-unique antigenic Hsp60 determinant, respectively, could thus be deduced to result from single **amino acid substitutions**. Analysis of the antibody response in patients' sera demonstrated reactivity with the same **fusion** polypeptides in six out of nine sera, indicating that neisserial Hsp60 is expressed during the natural infection and that distinct domains on the protein are immunodominant in vivo.

=> L3 and "antigen binding"
L10 3 L3 AND "ANTIGEN BINDING"

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L10 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:336158 CAPLUS
DOCUMENT NUMBER: 131:128760
TITLE: A peptide binding motif for I-Eg7, the MHC class II molecule that protects E.alpha.-transgenic nonobese diabetic mice from autoimmune diabetes
AUTHOR(S): Gregori, Silvia; Trembleau, Sylvie; Penna, Giuseppe; Gallazzi, Fabio; Hammer, Juergen; Papadopoulos, George K.; Adorini, Luciano
CORPORATE SOURCE: Roche Milano Ricerche, Milan, I-20132, Italy
SOURCE: Journal of Immunology (1999), 162(11), 6630-6640
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English
TI A peptide binding motif for I-Eg7, the MHC class II molecule that protects
E.alpha.-transgenic nonobese diabetic mice from autoimmune diabetes
SO Journal of Immunology (1999), 162(11), 6630-6640
CODEN: JOIMA3; ISSN: 0022-1767
AU Gregori, Silvia; Trembleau, Sylvie; Penna, Giuseppe; Gallazzi, Fabio; Hammer, Juergen; Papadopoulos, George K.; Adorini, Luciano
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:145401 CAPLUS
DOCUMENT NUMBER: 118:145401
TITLE: Functional analysis of DR17(DR3)-restricted mycobacterial T cell epitopes reveals DR17-binding motif and enables the design of allele-specific competitor peptides
AUTHOR(S): Geluk, Annemieke; Van Meijgaarden, Krista E.; Janson, Anneke A. M.; Drijfhout, Jan Wouter; Meloen, Rob H.; De Vries, Rene R. P.; Ottenhoff, Tom H. M.
CORPORATE SOURCE: Dep. Immunohematol. Blood Bank, Univ. Hosp., Leiden, 2300 RC, Neth.
SOURCE: Journal of Immunology (1992), 149(9), 2864-71
CODEN: JOIMA3; ISSN: 0022-1767
DOCUMENT TYPE: Journal
LANGUAGE: English
TI Functional analysis of DR17(DR3)-restricted mycobacterial T cell epitopes reveals DR17-binding motif and enables the design of allele-specific competitor peptides
SO Journal of Immunology (1992), 149(9), 2864-71
CODEN: JOIMA3; ISSN: 0022-1767
AU Geluk, Annemieke; Van Meijgaarden, Krista E.; Janson, Anneke A. M.; Drijfhout, Jan Wouter; Meloen, Rob H.; De Vries, Rene R. P.; Ottenhoff, Tom H. M.

L10 ANSWER 3 OF 3 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:462498 BIOSIS
DOCUMENT NUMBER: PREV199699184854
TITLE: A new member of the hsp90 family of molecular chaperones interacts with the retinoblastoma protein during mitosis and after heat shock.
AUTHOR(S): Chen, Chi-Fen; Chen, Yumay; Dai, Kang; Chen, Phang-Lang; Riley, Daniel J.; Lee, Wen-Hwa (1)
CORPORATE SOURCE: (1) Cent. Mol. Med./Inst. Biotechnol., Univ. Texas Health Sci. Cent. San Antonio, 15355 Lambda Dr., San Antonio, TX 78245 USA
SOURCE: Molecular and Cellular Biology, (1996) Vol. 16, No. 9, pp. 4691-4699.
ISSN: 0270-7306.
DOCUMENT TYPE: Article
LANGUAGE: English
TI A new member of the hsp90 family of molecular chaperones interacts with the retinoblastoma protein during mitosis and after heat shock.
SO Molecular and Cellular Biology, (1996) Vol. 16, No. 9, pp. 4691-4699.
ISSN: 0270-7306.
AU Chen, Chi-Fen; Chen, Yumay; Dai, Kang; Chen, Phang-Lang; Riley, Daniel J.;
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=> D L10 IBIB TI SO AU ABS 2

L10 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2002 ACS
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DOCUMENT NUMBER: 118:145401
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CORPORATE SOURCE: Dep. Immunohematol. Blood Bank, Univ. Hosp., Leiden, 2300 RC, Neth.
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CODEN: JOIMA3; ISSN: 0022-1767
AU Geluk, Annemieke; Van Meijgaarden, Krista E.; Janson, Anneke A. M.; Drijfhout, Jan Wouter; Meloen, Rob H.; De Vries, Rene R. P.; Ottenhoff, Tom H. M.
AB The authors have previously shown that p3-13 (KTIAYDEEARR) of the 65-kDa **heat shock protein** (hsp65) of Mycobacterium tuberculosis and M. leprae is selected as an important T cell epitope in HLA-DR17+ individuals, by selectively binding to (a pocket in) DR17 mols., the major subset of the DR3 specificity. They have now further studied the interaction between p3-13, HLA-DR17 and four different TCR (V.beta.5.1, V.beta.1, and V.beta.4) by using T cell stimulation assays, direct peptide-DR binding assays, and a large panel of the single

amino acid substitution analogs of p3-13.
Residues 5(Ile) and 8(Asp) of p3-13 are important DR17 binding residues, whereas the residues that interact with the TCR vary slightly for each DR17-restricted clone. By using N- and C-terminal truncated derivs. of p2-20 the minimal peptide length was defined for both HLA-DR17 binding and
T cell activation: the minimal peptide that bound to DR17 was seven amino acids long whereas the minimal peptide that activated T cell proliferation
was eight amino acids in length. Furthermore, two new DR17-restricted epitopes were identified on hsp70 and hsp18 of M. leprae. Alignment of the crit. DR17-binding residues 5(Ile) and 8(Asp) of p3-13 with these two novel epitopes and two other DR17-binding peptides revealed the presence of highly conserved amino acids at positions n and n + 3 with Ile, Leu, and Val at position n and Asp and Glu at position n + 3. Asp and Glu are particularly likely to interact with the DR17-specific, pos. charged pocket that was defined earlier. Based on these results, a set of single amino acid substituted analogs that failed to activate these T cell clones
but still bound specifically to DR17 was defined and tested for their ability to inhibit T cell activation by p3-13 or other DR17-restricted epitopes. Those peptides were able to inhibit the response to p3-13 as well as other DR17-restricted mycobacterial epitopes in an allele-specific
manner, and are anticipated to be of potential use for immunotherapeutic and vaccine design strategies.